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**Object-use and the left hemisphere:
the implications of apraxia and brain
stimulation on perception for action**

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PhD

2015

**Object-use and the left hemisphere:
the implications of apraxia and brain
stimulation on perception for action**

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the requirements of the University of
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Abstract

Apraxia, a high-level movement disorder, is associated with performance errors during gesture imitation, demonstrating the use of familiar objects that are present (actual object-use) or absent (pantomime), or all three scenarios. Focusing on objects, apraxia has an isolated effect on manipulation judgements regarding skilled object-use. These manipulation deficits are potentially attributed to damage to a purported ventro-dorsal stream resulting in impaired internal representations of movement (i.e. motor imagery). Instead, patients over-rely on visual affordances during object-directed motor behaviour. The cortical regions associated with the ventro-dorsal stream correspond to those damaged in apraxia, in particular the left inferior parietal lobe (IPL), adding weight to this proposal.

Using a perceptual matching task with familiar objects and an action execution grasping task with novel objects, behavioural work with left hemisphere stroke patients assessed whether apraxic deficits are specific to object manipulation and whether these patients over-rely on object affordances during skilled object-manipulation. In parallel, the effect of neuromodulation technique transcranial direct current stimulation (tDCS) on motor imagery was explored with healthy populations. Performance changes during left IPL stimulation was assessed during classic motor mental rotation and the same perceptual matching task used with patients.

Apraxic patients showed a selective impairment during object manipulation judgements of the perceptual matching task, which increased with apraxia severity. Despite tDCS over the left or right IPL equally affecting motor mental rotation performance in healthy populations, during the perceptual matching task only modulation of the left IPL slowed reaction times when making manipulation judgements but not functional semantic judgements regarding object-use. These results suggest that disruption of ventro-dorsal processing specifically disturbs motor representations of object-use. When repeatedly grasping novel objects of differing weight distribution, most apraxic patients consistently selected a structurally afforded grasp-point, indicating that apraxic patients over-rely on visual affordances after ventro-dorsal disruption.

These results confirm that the ventro-dorsal stream, in particular the left IPL, is critical in integrating perceptual internal representations of skilled movement into context-dependent action plans based on visual information. Over-reliance on visual affordances caused by disruption to this pathway not only affects perceptual manipulation judgements of familiar objects but also experience-based learning when grasping novel objects.

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Declaration

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

Any ethical clearance for the research presented in this thesis has been approved. Approval has been sought and granted by the Faculty of Health and Life Sciences ethics committee at the University of Northumbria in Newcastle.

I declare that the Word Count of this Thesis is 48,747 words

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Chapter 1

General Introduction

Over the years, neuropsychology has given us detailed insight into the functional processes in the brain. Clinical populations have offered support for current theory and opened new questions. Apraxia is a particular example of a condition that has both enlightened and puzzled researchers for many years. By dissecting the functions maintained and disturbed in apraxia, the condition has recently been suggested to reflect impaired internal representations of movement (i.e. motor imagery) that are attributed to disruption to a purported ventro-dorsal sub-stream of the visual pathways model. However to date this claim has rarely been directly assessed. With particular emphasis on apraxic patients' understanding of object-use, the current thesis explores the dissociable impairments in apraxia, from perception of object-use to skilled action execution, to establish whether their behaviour asserts this proposal.

The current thesis also directly explores the neural correlates of internal representations of movement. As localising function through patient research is not straightforward, the neuromodulation technique transcranial direct current stimulation (tDCS) was used with healthy populations. Both classic and novel motor imagery tasks established whether stimulation of the inferior parietal lobe, supposedly implicated in the ventro-dorsal stream, would modify motor imagery performance. In particular, whether the left inferior parietal lobe has a dominant role in generating movement representations, as is often assumed. These studies offer a direct link between motor imagery and the left IPL, and also inform theories regarding the cause of apraxia. The amalgamation of neuropsychological and neuromodulatory methods in this thesis allowed comprehensive investigation of perception for action.

In the first part of this introductory chapter, a general overview of the three key components of the current thesis will be outlined: apraxia, motor imagery, and the ventro-dorsal sub-stream of the visual pathways model. The introduction will define each component and describe how they interlink. Particular emphasis will be paid to object-use errors observed in apraxia and how they have led to the suggestion of disrupted internal movement representations due to damage to the ventro-dorsal sub-stream of the visual pathways model.

The second part of this general introduction will detail the two methodological techniques used in this thesis, clinical research with left hemisphere stroke patients and brain stimulation with

healthy participants. Particular emphasis is paid to how these techniques support the questions that functional neuroimaging cannot answer by allowing causal associations to be made between brain structure and function. As tDCS has been seldom used in this research field, assumptions regarding the physiological effects of the technique shall also be discussed.

1.1. Apraxia

Originally reported by Liepmann in the early twentieth century, apraxia is defined as a higher order motor impairment in which patients display deficits in skilled movements that cannot be attributed to a primary sensory or motor deficit (Buxbaum, 2001). Although apraxia is a broad term that is applied to several impairments, there are generally accepted core symptoms that appear singularly or in combination. These typically occur following left hemisphere lesions and affect both sides of the body.

Gesture Imitation. Apraxic patients show defective imitation of gestures that are performed by a model (Haaland & Flaherty 1984; Haaland, Harrington, & Knight, 2000; Buxbaum, Johnson-Frey, & Bartlett-Williams, 2005; Buxbaum, Kyle, Grossman, & Coslett, 2007). Often errors are spatiotemporal in nature, being performed in an inappropriate plane relative to the body (see Figure 1.1 for example). Imitation errors can be body-part specific, with dissociable performance identified when imitating gestures with the hands, fingers, or feet. Left parietal lesions robustly affect hand gesture imitation whereas impaired imitation of finger and foot gestures can also result from lesions to the left frontal cortex or right hemisphere (Goldenberg, 2014). Interestingly, imitation errors manifest when replicating gestures on a manikin or when selecting matching photographs of gestures (Goldenberg, 1995; Goldenberg, 1999). Apraxic patients also fail to recognise pantomimed actions, or to identify their own actions from those performed by others (Sirigu, Daprati, Pradat-Diehl, Franck, & Jeannerod, 1999) indicating that imitation errors extend beyond movement execution to movement perception.

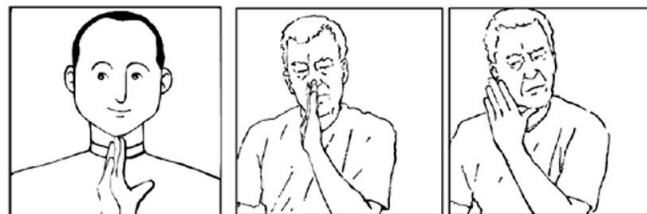


Figure 1.1. Example of imitation errors observed in apraxia.

When copying meaningless hand postures, the left image shows the model gesture, the middle image shows a stage in the searching movements and the right image the final position. Image taken from Goldenberg (2013).

Pantomime. Deficits are also apparent when apraxic patients are asked to produce meaningful gestures on command, including symbolic actions such as “how to salute” or pantomiming object-use such as “how to use a hammer”. Pantomime errors range from failure to assume appropriate hand position and body orientation in relation to tools, poor coordination of movement parts, and substitution, omission, and body-part-as-object errors (using their body parts as if they were objects, such as brushing teeth with the index finger). On the whole, execution of these movements is associated with spatial and temporal errors, which are more apparent in tasks involving transitive gestures compared to intransitive (Goldenberg, 1995).

Actual object-use. In severe cases, the errors observed in pantomime of object-use can also be observed during actual use of objects. Performance during actual object-use often separates two forms of apraxia, ideational and ideomotor apraxia. Ideational apraxia is considered a loss of *ideation*, resulting in conceptual deficits; patients display a loss of knowledge of the movements associated with objects that affects pantomime and executed object-use, particularly during multiple object tasks such as preparing a cup of tea. It is believed that these apraxic patients are unable to associate familiar objects with their corresponding action and may also fail to identify the typical function of the object (Leiguarda & Marsen, 2000). These deficits often occur when posterior temporal-parietal regions are compromised due to implicating semantic regions in the brain (De Renzi & Lucchelli, 1988; Buxbaum & Saffran, 2002). Unlike ideational patients, ideomotor apraxics show spatiotemporal errors during pantomime but show mild impairments or relatively normal object-use during action execution. These patients are often described as knowing what to do but not how to do it (Goldenberg & Hagmann, 1998; Halsband et al., 2001; Sunderland & Shinner, 2007; Ietswaart & Milner 2009). Improvement during actual object-use has been proposed to be due to reduced task difficulty, with contextual information cueing the appropriate action. Nevertheless subtle kinematic abnormalities during movements within natural contexts coupled with correlation in pantomime performance and actual object-use confirms that performance is improved but not normal during action execution (Clark et al., 1994; Foundas et al., 1995). Although the frontal lobes have been implicated, the left inferior parietal lobe (IPL) has consistently been associated with ideomotor apraxia (Haaland et al., 2000; Leiguarda & Marsen, 2000; Goldenberg, 2009). Figure 1.2 gives an example of object-use errors observed in apraxia.

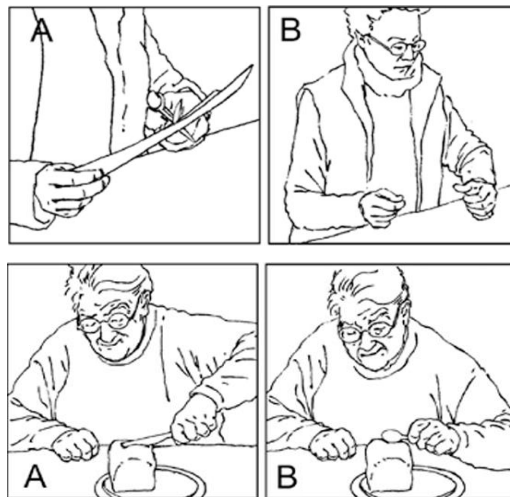


Figure 1.2. Examples of object-use errors in apraxia.

Top (A) an apraxic patient demonstrating the appropriate use of scissors and paper when the objects are present. (B) The patient pantomiming the use of scissors and paper when the objects are absent. Bottom (A) patient appropriately cutting bread with a knife. (B) Demonstrating inappropriate object-use by attempting to cut bread with a spoon. Images taken from Goldenberg (2013).

In contrast to impaired pantomime and execution of functional based object-use described above, apraxic patients show intact reach and grasp action when object function is not task relevant (Ietswaart, Carey, & Della Sala, 2006). As these movements do not depend on high-level cognitive processes, the confinement of apraxic symptoms to skilled action has led to the assumption that apraxia is strongly related to cognitive aspects of motor control. Although the cause of apraxia is relatively unknown, it is suggested that the core deficits reflect deficient generation of internal representations of movement, also known as motor imagery (Buxbaum, 2001). Not only are these representations implicitly activated when planning an executed action, but also when explicitly simulating movement. This proposal may explain why apraxic errors manifest not only in executed behaviour but also in cognitive tasks calling upon similar processes. Despite the selective deficits of apraxic patients suggesting that motor imagery may be impaired, researchers seldom refer to motor imagery in relation to apraxic symptoms. Moreover, few studies have carefully teased apart what is disturbed and maintained in these patients to assess whether there is a relationship between motor imagery integrity and apraxia. Critical evaluation of this relationship is necessary in order to confirm whether apraxia results from disturbance to internal movement representations.

1.2. Motor Imagery

Internal representations of movement, or motor imagery, can be generalised as the mental simulation of a motor act in the absence of overt movements (Crammond, 1997; Jeannerod, 1994). It is described as an imagined movement from the first person perspective and is considered critical for the implicit or explicit planning of movement, passive observation of action, mental operations of sensorimotor representations, and action imitation (Annett, 1995; Lotze & Halsband, 2006). During explicit motor imagery, the imager has both a visual and kinaesthetic sensation of him or herself performing the movement. This differs from imagining movement from the third-person perspective, which relies on visual resources and is considered visual imagery (Annett, 1995; Sirigu & Duhamel, 2001; Munzert, Lorey, & Zentgraf, 2009).

It is generally assumed that motor imagery utilises many of the same neural correlates as motor execution. Specifically, it is believed that motor imagery forms part of the representational stages of action (Jeannerod & Decety, 1995; Mulder, 2007). Neuroimaging data supports this proposal with activity in a complex network of visuomotor areas during motor imagery. These include motor, premotor, occipital, temporal, and parietal areas (Decety et al., 1994; Decety, 1996; Sirigu, Duhamel, & Cohen, 1996). Of particular interest, consistent activation is observed in inferior parietal regions. These areas are also active during object-related movement, with activation present during tasks involving imagined grasping movements, perceptually based decisions and prospective action judgements, visual presentation of graspable objects, and retrieval of postural requirements related to object-use (Buccino et al., 2001; Buccino, Binkofski, & Riggio, 2004; Rizzolatti & Craighero, 2004; Rumiati et al., 2004; Caspers, Zilles, Laird, & Eickhoff, 2010; Wadsworth & Kana, 2011).

In addition to recruiting similar cortical areas as actual movement, behavioural data indicates that imagined action retains the same characteristics as action execution; motor imagery is affected by an individual's actual body posture, the biomechanical constraints and inertial properties of the limb being simulated, and also the temporal characteristics corresponding to the real action (Jeannerod, 2001). For example, imagined movement conforms to Fitts's Law of the inverse relationship between movement difficulty and time taken to perform. In other words, the more difficult a movement is to perform, the longer it takes to complete it, both in imagery and action execution. Decety and colleagues confirmed that when imagining walking along beams of varying width, imagined walking time increased with task difficulty; participants took longer to imagine walking down narrow beams consistent with their behaviour during actual movement (Decety & Jeannerod, 1996). Tasks typically used to examine motor imagery include the laterality judgement task and mental chronometry. During the laterality judgement task, where participants must indicate whether the left or right hand is presented, time taken to respond corresponds with Fitts's

law and the biomechanical constraints of the hand posture; response times are slower when the posture is more difficult to perform or when the hand being imagined is restricted or impaired (Sekiyama, 1982; Parsons, 1987; Decety & Jeannerod, 1996; Nico, Daprati, Rigal, Parsons, & Sirigu, 2003). Further, during mental chronometry, where participants must execute and imagine completing thumb-finger opposition movements to a metronome, the fastest metronome speed at which the participant can maintain the finger tapping sequence corresponds during real and imagined movement (Sirigu et al., 1995; Sirigu et al., 1996; Crammond, 1997).

Motor imagery has also been closely linked to action observation. Based on the mirror neuron network theory established in primate research, the same visuomotor neurons that discharge during action execution are also active during action observation (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992; Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti et al., 1996; Buccino et al., 2001). Although heavily debated, it has been theorised that mirror neuron activity mediates imitation (Jeannerod, 1994) and forms the basis of action understanding (Rizzolatti, Fogassi, & Gallese, 2001). The existence of mirror neuron networks in humans is supported by neuroimaging data, with action observation implicating visuomotor regions, including the precentral gyrus, inferior frontal gyrus, and IPL in particular (Buccino et al., 2001; Decety, Chaminade, Grèzes, & Meltzoff, 2002; Rizzolatti & Craighero, 2004; see Caspers et al., 2010 for meta-analysis of areas implicated in action observation). Although the role of corresponding activity is unknown, such neuroimaging and behavioural data offer substantial evidence that action observation, motor imagery, and movement execution rely on similar neural networks. Crucially, motor imagery appears to form a critical part in the perception of movement and motor preparation.

1.3. Motor imagery and apraxia

Given the necessity of internal movement representations in motor execution and simulation, motor imagery is ideal for evaluating the integrity of these representations in apraxia. If apraxia is attributed to impaired motor representations, then performance should be poor in tasks requiring motor imagery, but appropriate in tasks where motor imagery is not necessary. Although some research has explored dissociations in apraxic patients performance during object-related tasks, these have rarely been approached from a motor imagery perspective.

During perceptual tasks calling upon motor imagery, apraxic patients display abnormal behaviour. In addition to impaired pantomime, apraxic patients also fail to recognise pantomimed actions, comprehend the meaning of pantomimes, or to identify their own actions from those performed by others (Rothi, Heilman, & Watson, 1985; Sirigu et al., 1999). Further, motor imagery is impaired when simulating movement with the affected limb; a patient with parietal

cortex damage reported that when simulating movement there was a sensation of mental drag that matched the limbs reduced motor efficiency (Sirigu et al., 1995; Sirigu et al., 1996). Referring to the classic tasks used to examine motor imagery, apraxic patients display errors. During the hand laterality judgement task, patients with apraxia appear to show a selective deficit when mentally rotating hands, while mental rotation of objects is maintained (Tomasino, Rumiati, & Umiltà, 2003a; Tomasino, Toraldo, & Rumiati, 2003b; Overney & Blanke, 2009). The latter task is not reliant on motor but visual imagery, calling upon predominantly visual areas. Sirigu and colleagues (Sirigu et al., 1995; Sirigu et al., 1996) also found that during mental chronometry, apraxic patients' imagery of the thumb-finger opposition movement did not match their actual movements when patients suffered from lesions to the parietal but not motor cortex.

1.4. Apraxia and object-use

Of particular relevance to the current thesis, evidence indicating apraxia may be associated with impaired motor imagery arises from research assessing errors relating to the typical use of familiar objects. In particular, perceptual tasks enable different aspects of object knowledge to be explored that are otherwise difficult to separate during motor execution. These tasks suggest that apraxic patients may have a selective deficit perceiving the motoric elements of object-use, supporting the notion that these patients often know what to do, but not how to do it.

Firstly, patients with apraxia can recognise and identify visually presented objects (Daprati & Sirigu, 2006), and order familiar objects in weight order (Dawson, Buxbaum, & Duff, 2010; Li, Randerath, Goldenberg, & Hermsdörfer, 2011), indicating that semantic representations of familiar objects are maintained. Apraxic patients also appear to have maintained perception of the function of familiar objects (i.e. what an object is used for); when required to pair objects that have a similar function (such as a matchstick and lighter being used to make a flame), apraxic patients perform appropriately. This suggests that object-use errors in apraxia cannot be attributed to impaired representations of the functional purpose of familiar objects (Buxbaum & Saffran, 2002; Myung et al., 2010). However, apraxic patients perform abnormally when making manipulation judgements (i.e. how an object is typically used) regarding familiar objects, incorrectly producing and recognising the correct hand posture required to perform transitive movements (Buxbaum & Saffran, 2002; Buxbaum, Sirigu, Schwartz, & Klatzky, 2003; Buxbaum et al., 2005; Daprati, Nico, Duval, & Lacquaniti, 2010; Myung et al., 2010). This behaviour not only indicates that object knowledge is 'modality-specific' and represented across different parts of the brain, but also suggests that apraxic errors are closely related to motoric elements of object-use. Crucially, these selective deficits strongly support the proposal that apraxic patients have impaired motor representations that are necessary when making manipulation judgements. Yet, if apraxia is associated with a selective impairment in motoric action representations, then non-

motoric action representations, such as the movement of the hammer hitting the nail, must remain intact. This would further indicate that motoric and non-motoric object-related actions are processed separately in the brain. As this has yet to be explored, the first empirical chapter of the current thesis will assess whether apraxic errors are confined to motoric action.

Interestingly, apraxic patients have been suggested to effectively use structural properties when manipulating objects, using an object's visual affordances to inform action. Affordances are defined as features of an object that trigger potential actions relevant to the goal of the motor act. During skilled object-use, actions are afforded by both the structural properties of the object and stored representations regarding its functional purpose. Depending on whether an object is grasped for transfer or for use, different actions are facilitated (Gibson 1979; Cisek 2007). As described, apraxic patients have maintained stored representations (semantic and function perception) but make errors when these intact representations must be incorporated with motor representations, in the case of manipulation judgements or functional grasps for skilled use. However, patients with apraxia do use visible affordances to infer the function of novel objects and appropriately grasp objects for transfer (Sirigu et al., 1995; Goldenberg & Hagmann, 1998; Buxbaum et al., 2003; Ietswaart et al., 2006; Randerath et al., 2009; Randerath, Goldenberg, Spijkers, Li & Hermsdörfer, 2010; Sunderland, Wilkins, Dineen, & Dawson, 2013). The maintained ability to utilise visual affordance information is proposed to bias behaviour towards structural rather than functional grasps during object manipulation (Randerath, Goldenberg, Spijkers, Li, & Hermsdörfer, 2011). Correct use of visually afforded cues compliments appropriate non-functional grasping (Randerath et al., 2009; Ietswaart et al., 2006) and research indicating that object-use performance improves with increased contextual information from pantomime, demonstration and actual object-use (Randerath et al., 2011).

Notably, in a series of sophisticated reach and grasp tasks Creem and Proffitt (2001) found that stored representations from the cognitive system influenced object-directed action in healthy participants even when this information is not relevant to the movement goal. When the handle of a familiar object was oriented away from participants, grasps were frequently directed towards the handle in an appropriate manner for their typical use even if this resulted in a more awkward grasp. Their data confirmed that motor and cognitive representations were not only distinct but also interact. However, when a similar task was given to apraxic patients, non-functional grasps were chosen regardless of whether objects were being grasped for use or for transfer, suggesting that stored semantic representations were not being successfully integrated into the action plan (Randerath, Li, Goldenberg, & Hermsdörfer, 2009). Collectively, preserved use of visual affordance cues and impaired integration of stored representations suggests that apraxic errors

may not only be specific to motoric elements of action, but also dependent on the type of motoric action being performed.

Referring to manipulation of novel objects, performance errors suggest that impaired motor imagery may disrupt the integration of long-term stored representations into short-term action plans, but also affect actions reliant upon the conceptual stages of action that cannot be completed on the basis of visual affordance information. The novel tools test used by Goldenberg and colleagues (Goldenberg & Hagmann, 1998; Goldenberg & Spatt, 2009) indicates that apraxic patients are impaired when selecting a tool best suited for manipulating a cylinder. Appropriate tool selection requires generation of an internal representation of movement to assess whether the goal of lifting the cylinder can be achieved with a given tool. Consistent with previous research, lesions implicating frontoparietal regions including frontal areas such as the middle frontal and inferior frontal gyri, and parietal lesions implicating the supramarginal gyrus through inferior to superior parietal regions were impaired on novel and familiar tool-use (Goldenberg & Spatt, 2009), suggesting motor imagery is indeed disrupted. Other tasks involving novel objects have found similar deficits when apraxic patients are required to solve mechanical puzzles (Heilman et al., 1997), use familiar objects in an unusual way (Osiurak et al., 2009; Sunderland, Wilkins, & Dineen, 2011), or during actual and imagined grasping of dowels and widgets (Buxbaum et al., 2005).

Together, apraxia appears to not only affect the generation and retrieval of internal representations for familiar object-use, but also the ability to skilfully manipulate novel objects. Based on these findings, object-use errors in apraxia seem to depend on the goal of the motor act, manifesting when stored representations regarding objects from the semantic system must be integrated into action plans, or when actions are heavily reliant upon conceptual stages of action to allow skilled manipulation of objects as opposed to simply grasping to move or on the basis of visual affordance cues.

Although the selective deficits in apraxia appear to point to motor imagery impairment, this is not yet certain. Amongst others, Goldenberg claims the theory that skilful object manipulation relies on the integration of visible and known properties of objects places too much importance on the different components of object knowledge (Goldenberg, 2013). The criticisms Goldenberg describes are based on the notion that a “core” gesture representation exists for each familiar object that contains invariant and critical features of the movement. For example, the gesture representation for “hammering” contains the movements of the arm and posture of the hand, which differs from the representation for using a screwdriver. Retrieval of motor representations of an objects prototypical use depends on previous experience, which can only be attributed to

impaired use of familiar objects and does not account for apraxic errors during novel object-use (as in the novel tools test for example). The suggestion of impaired access to stored “core” representations also does not account for the inability to use familiar objects for an alternative purpose based on their functionally significant parts (such as using a knife as an alternative to a screwdriver due to the shape and thickness of the blade). Instead of impaired retrieval of instructions of use from semantic memory, Goldenberg and colleagues proposed that apraxia impairs mechanical problem solving in individuals who make errors in object-use, disturbing the ability to infer an object's function from structure (Goldenberg & Hagmann, 1998; Goldenberg, 2013). Goldenberg argued that there is no need for additional “manipulation knowledge” specifying the configuration of the hand that is applied to the familiar object, but rather individuals apply mechanical problem solving depending on task requirements by identifying the functional capabilities of the object (i.e. a knife can replace a screwdriver). He argues that the ability to apply mechanical problem solving is disturbed in apraxia.

Goldenberg rightfully points out that it would be wasteful to have one prototypical representation for each object. However his supposition that “manipulation knowledge” assumes “storehouses” of core representations overshadows the definition of manipulation knowledge, or motor representations, as a flexible high-level praxis system in which representations are activated and integrated depending on task demands. The suggestion of a high-level praxis system stems from Heilman and colleagues’ (Heilman, Rothi, & Valenstein, 1982) early proposal that motor acts can be separated: those requiring retrieval of information from memory (in the case of typical use of familiar objects for example) and those constructed *de novo*. Heilman suggested that apraxia results from a loss of stored representations of learned movements; if the motor memory for appropriate object-use is destroyed, this account offers an explanation for dissociations in the ability to grasp objects for transfer whilst skilled object-use is impaired. Despite the notion of dissociable motor acts being generally supported Heilman’s proposal unfortunately falls short, as it can only account for apraxic errors during the perception or use of familiar objects. Similarly, if stored representations of learned movements were destroyed, performance would not differ with increased contextual information contradicting the dissociable performance during pantomimed compared to executed action that is typically superior.

Based on Heilman’s early model, it seems more reasonable to consider “manipulation knowledge” as high-level movement representations that are disconnected from the rest of the visuomotor network rather than lost (Haaland et al., 2000; Buxbaum & Saffran, 2002). If an appropriate movement were planned on the basis of an amalgamation of information from different functional sources such as sensory, motor, and semantic systems, then disturbance in this integrative process would result in an ill-informed motor plan leading to an inaccurate

movement. The resultant disturbance in the integration of known and visible properties would account for apraxic errors during the perception and execution of familiar and novel object-related movement. Skilful object-use, whether the object is familiar or novel, still requires long-term movement representations to be generated to assess the appropriateness of the planned movement to achieve the action goal. Such planning differs from grasping objects for transfer that is only reliant on short-term movement representations allowing appropriate grip scaling based on visual affordance information. Equally, impaired integration of perception for action would account for the improved performance during actual object-use compared to pantomime in apraxia; pantomime of object-use places greater demand on cognitive mechanisms that may be disconnected, thus resulting in more action errors. Increased contextual information in the environment during actual object-use reduces demand on the conceptual system leading to improved performance (Clark et al., 1994; Foundas et al., 1995; Randerath et al., 2011).

Substantial support for the notion of dissociable motor acts that call upon information from different functional systems stems from research exploring the neural correlates of the visuomotor network. This research indicates the presence of dissociable pathways important for different types of movement. Most crucially, the selective impairments observed in apraxic patients during skilful object-use, whilst non-functional object manipulation is maintained, informs theories regarding the division of labour in the visual pathways model and supports the recent proposal of an additional sub-stream that may be critical for the integration of perception for action. This purported sub-stream may be crucial when generating internal movement representations necessary for skilled action.

1.5. The visual pathways model

The visual pathways model was originally developed through primate research. In the macaque monkey Ungerleider and Mishkin (1982) identified two broad ‘streams’ of projections from visual areas. A “dorsal” visual stream projecting from primary visual areas to posterior parietal cortex, and a “ventral” visual stream projecting from primary visual areas to inferior temporal regions. These anatomically segregated streams were suggested to have different but complementary roles in the processing of incoming visual information. When the inferior temporal cortex was lesioned, the monkey could no longer discriminate between objects based on their visual features, but could perform appropriately during the spatial landmark task where reward location was indicated by a visual cue. Lesions to the posterior parietal cortex however produced deficits in the landmark task whilst object discrimination was unaffected (Goodale & Milner, 1992). This led to the proposal that the dorsal visual stream, or “where” pathway, was dedicated to processing spatial information of where an object is located in space, whereas the ventral stream, or “what” pathway, mediated object identification.

Later research by Milner and Goodale (Goodale & Milner, 1992) however suggested these dissociable visual pathways both manipulated information about the nature of objects and their location in space. It was argued that separate processing of object identity and the location it occupies was counterintuitive. Instead, it was proposed that the ventral and dorsal streams both process an objects' intrinsic (shape, texture, colour) and extrinsic (locations and movement) properties, but for different purposes (Frey, 2007). The dorsal *vision-for-action* stream, now known as the “how” pathway, mediates the visual control of skilled action using intrinsic and extrinsic properties to guide actions on a moment-to-moment basis. The most direct visual pathway for action, the dorsal stream transforms information “online” to the motor system allowing immediate reaching and grasping (Goodale & Milner, 1992; Milner & Goodale, 2008; Singh-Curry & Husain, 2009). In humans it is generally believed that the dorsal stream projects bilaterally from visual to superior parietal and dorsal pre-motor areas. The ventral *vision-for-perception* stream on the other hand transforms visual inputs into perceptual representations to support object recognition and semantic processing. A more indirect route to the motor cortex, the ventral stream is suggested to embody the long-term characteristics of objects allowing movement planning based on the memory of an object (Goodale, 1998; Goodale & Milner, 1992; Buxbaum & Kalénine, 2010). This stream extends from occipital to inferior temporal regions.

Alternatively, recent evidence suggests that the visual pathways are not dichotomous, but in fact may possess an additional sub-stream known as the “ventro-dorsal” pathway. It is the functional role of this purported sub-stream that is of particular interest to the thesis. Based on the neurophysiological evidence in the monkey, Rizzolatti and Matelli (2003) refined the visual pathways model by proposing that the dorsal stream had in fact two distinct functional systems: the ‘dorso-dorsal’ stream and the ‘ventro-dorsal’ stream. The dorso-dorsal stream is equivalent to Milner and Goodale’s traditional dorsal pathway, controlling action online and involving the superior parietal and dorsal premotor regions (Kalénine, Buxbaum, & Coslett, 2010; Rizzolatti, Fogassi, & Luppino, 2011). The ventro-dorsal stream however is thought to be important for space perception and action understanding. It represents the core features of object-use actions and articulates action and object knowledge. This remains distinguished from the ventral system (Kalénine et al., 2010). Unlike the dorsal pathway, the ventro-dorsal stream incorporates long-term action representations required for skilled movement through reciprocal connection to the ventral pathway via the IPL. This information is then projected to portions of the posterior temporal lobe, ventral premotor cortex, and frontal eye field (see Figure 1.3 for schematic view of the cortical projections of each pathway). Crucially, it is suggested that reliance on either the dorsal or ventro-dorsal sub-streams is dependent on the *goal* of the motor act. Considered as the “structure” or “grasp” system, the dorsal stream relies on structural based object properties to

allow appropriate selection of prehensile actions to reach and grasp objects for transfer. Alternatively, the ventro-dorsal “function” or “use” system utilises stored representations allowing objects to be manipulated for skilled action (Buxbaum & Kalénine, 2010; Binkofski & Buxbaum, 2013; Vingerhoets 2014).

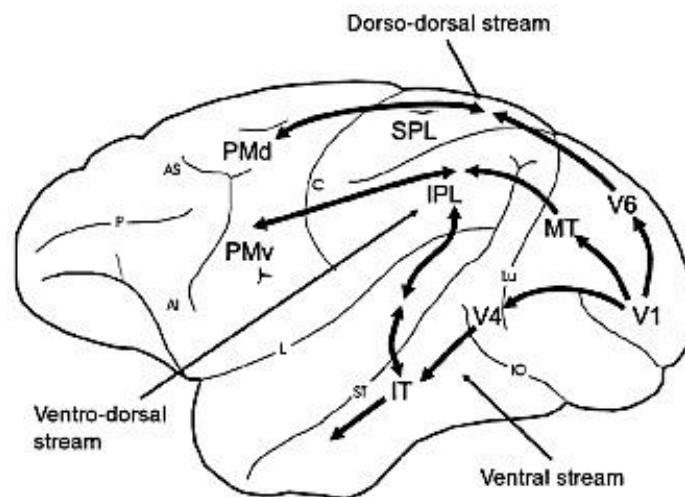


Figure 1.3. A schematic view of the cortical visual streams.

According to Rizzolatti and Matelli (2003) the dorso-dorsal stream extends from the primary visual cortex (V1), to V6, superior parietal lobe (SPL), and dorsal premotor cortex (PMd). Vento-dorsal processing projects from V1 to the middle temporal area (MT), to inferior parietal lobe (IPL), and ventral premotor cortex (PMv). The ventral pathway extends from V1 to V4, to inferior temporal (IT) regions. Also illustrated is the reciprocal connection between ventro-dorsal and ventral streams. Image taken from Rizzolatti, Fogassi, & Luppino, 2011.

1.6. The relationship between apraxia, the ventro-dorsal stream, and the left inferior parietal lobe.

Although recent anatomical data offers substantial support for a ventro-dorsal stream, the potential relationship between this pathway and apraxia has rarely been considered. The current thesis therefore not only examined apraxia from a motor imagery perspective by confirming whether errors are confined to the motoric stages of action, but also with respect to whether errors are restricted to movements reliant on the integration of perception for action.

As described previously, apraxic patients can identify familiar objects and appropriately grasp objects for transfer. Applying these behaviours to the visual pathway model, maintained performance in these tasks confirms that apraxic patients have intact ventral and dorsal streams (Daprati & Sirigu, 2006; Vingerhoets 2014). Selective impairment when stored representations

must be integrated into action plans for appropriate functional manipulation of objects adds weight to the proposal of a dysfunctional ventro-dorsal stream in these patients. Disturbance of this sub-stream may result in impaired generation of internal movement representations where visible and known properties of objects must be integrated. Yet, Ietswaart and colleagues (Ietswaart, Carey, Della Sala, & Dijkhuizen, 2001) indicated that apraxic patients could successfully make memory-driven reach and grasp movements that are also believed to rely on the integration of stored ventral representations into dorsal action plans. Therefore disturbed incorporation of stored representations may depend on the complexity of the movement and whether they are heavily reliant on the integration of information from semantic regions.

In addition to selective action deficits during skilled movement, the cortical regions implicated in apraxia correspond to those reported to be part of the ventro-dorsal stream. As outlined by Rizzolatti and colleagues (2011), the ventro-dorsal pathway projects from primary visual areas to middle temporal and inferior parietal regions. These correspond to regions along the visuomotor network that are active during motor imagery, particularly during object-related movement (Decety et al., 1994; Rumiati et al., 2004; Caspers et al., 2010; Wadsworth & Kana, 2011). Of interest to the current thesis is the role of the inferior parietal lobe. Specifically, the ventro-dorsal stream is purported to be left lateralised, with the left IPL forming the critical juncture where stored representations and sensory-motor information is integrated (Frey, 2007; Vingerhoets, 2014). Apraxia typically manifests from left hemisphere lesions along the visuomotor network, especially after damage to the left IPL. The correspondence of cortical regions implicated in the ventro-dorsal stream and in apraxia offers substantial support for the proposal that the two are related. If the left IPL is compromised this may prevent stored representations from the ventral pathway being incorporated into the action plan. The subsequent movement would therefore be largely generated based on intact dorsal processing, potentially resulting in an overreliance on visual information of object structure. This corroborates apraxic patients ability to utilise visual affordance information to grasp objects and infer their function on the basis of their shape.

Although the left IPL is implicated in motor imagery within the ventro-dorsal stream, these representations also activate other cortical regions across the visuomotor network. Likewise, despite apraxia being heavily associated with left IPL lesions (as detailed earlier in this introduction), apraxic symptoms can manifest from damage to different cortical areas. Therefore, the critical role of the left IPL in this integrative process is uncertain. Firstly, impairments in gesture recognition and pantomime of object-use has been observed when lesions occur outside of the parietal lobe. When testing 33 left brain damaged patients (21 of which had apraxic symptoms) Pazzaglia and colleagues (Pazzaglia, Smania, Corato, & Aglioti, 2008) found that impaired gesture comprehension for familiar transitive and intransitive gestures correlated with

damage to the inferior frontal gyrus, but not the IPL. Similarly, a lesion mapping study by Goldenberg and colleagues (Goldenberg, Hermsdörfer, Glindemann, Rorden, & Karnath, 2007) showed that deficient pantomime of object-use was also associated with damage to the inferior frontal gyrus, whereas object-use pantomime was similar for patients with and without parietal lesions. Of note, as lesions extended into the underlying white matter it remains possible that pantomime errors were due to damage of projections to or from cortical regions including the IPL. Yet theta-burst stimulation over the left inferior frontal cortex of healthy participants impaired the production of transitive and intransitive gestures, while stimulation of the left inferior parietal lobe did not significantly affect gesture production (Bohlhalter et al., 2011). It was argued that posterior parietal regions support the selection and use of objects, whereas gesture production may depend more critically on the left inferior frontal cortex.

Although these findings call into question the necessity of left inferior parietal regions in object-use action, it is likely that both frontal and parietal regions play an important role in motor imagery processes but for different reasons. One explanation for largely frontal activation is that the inferior frontal gyrus stores the “vocabulary” of motor actions (Binkofski et al., 2000; Rizzolatti & Luppino, 2001), translating information about object properties and action goals into motor programs. Frontal regions are also associated with “utilisation behaviour” where lesions result in difficulty resisting the impulse to manipulate objects presented in the visual field and within reach (Lhermitte, 1983; Decety et al., 1997). Such disinhibition would also interfere with the ability to make choices between closely related alternatives, for example when each objects function and manner in which they are manipulated are highly similar (Goldenberg et al., 2007). That said predominant frontal activation in the absence of parietal lobe activity is in direct contrast with other research emphasising a major role of parietal regions, in particular the IPL in gesture and object-use understanding (Buxbaum et al., 2005; Weiss, Rahbari, Hesse, & Fink, 2008; Goldenberg 2009; Vingerhoets, 2014).

Similarly, although it is generally believed that internal movement representations are predominantly left lateralised in inferior parietal regions, the laterality debate remains largely unanswered, particularly when referring to pantomime and actual object-use. Left IPL activation has been confirmed when healthy individuals pantomime the use of objects, or retrieve knowledge about hand and finger movements related to object-use (Moll et al. 2000; Choi et al. 2001; Kellenbach, Brett, & Patterson, 2003; Rumiati et al. 2004; Ohgami et al. 2004; Johnson-Frey et al. 2005; Fridman et al. 2006; Buxbaum et al., 2006; Canessa et al., 2008; Frey 2008; Randerath et al., 2011; Vingerhoets et al., 2012). However, a clear association between parietal lesions and pantomime errors is not robust. As described, apraxia can manifest from lesions across the visuomotor network, including regions external to the left IPL. For example, a case study has

been reported of a left-handed patient who suffered from ideational apraxia after a right hemisphere lesion. This patient could name and point to familiar objects on command, but performed poorly when matching objects of a similar function or performing the correct object-associated movement (Ochipa, Rothi, & Heilman, 1989). Similarly, left and right brain damaged patients have shown equal impairment when performing the naturalistic actions of preparing a cup of coffee and fixing a cassette recorder (Hartmann, Goldenberg, Daumüller, & Hermsdörfer, 2005). However, the authors argued that these errors manifested for different reasons; right brain damaged patients struggled to follow multi-step actions believed to be due to deficits in attention, whereas left brain damaged patients errors demonstrated defective retrieval of functional representations and failure to problem solve through trial and error.

Despite apraxic symptoms manifesting from left or right parietal lesions, damage to left parietal regions results in bilateral object-use errors whereas right parietal damage often only result in contralesional impairments (Sirigu et al., 1996; Buxbaum et al., 2005). Further, there is considerable evidence that maintains the critical role of the left IPL. A recent meta-analysis by Niessen and colleagues (2014) confirmed a predominant involvement of the left IPL during pantomime of object-use, with 60% of lesion studies confirming parietal lesions lead to impaired pantomime, suggesting the IPL holds greater importance in pantomime than the inferior frontal gyrus. This lateralised activity during object-use pantomime is purportedly stronger in right-handed individuals compared to left-handers (Vingerhoets et al., 2012). Application of repetitive transcranial magnetic stimulation (rTMS) to the left IPL has also been shown to slow judgements regarding object manipulation, adding weight to the meta-analysis (Ishibashi, Lambon Ralph, Saito, & Pobric, 2011). These data support other research confirming object-use errors in patients with lesions implicating the left IPL (Leiguarda et al., 2001; Tomasino et al., 2003a; Tomasino et al., 2003b; Buxbaum et al., 2005; Kalénine et al., 2010). However, the uncertainty of these results, particularly when observing clinical data, suggests that the left IPL may not be the critical juncture where stored representations are integrated into action plans. It was suggested that when sensorimotor feedback is available, object-use pantomime is bilaterally modulated by superior parietal regions and two specific regions within the IPL (Vingerhoets, 2014). It may be more appropriate to suggest that additional frontal or white matter damage is necessary to disrupt pantomime and/or actual object-use (Vingerhoets et al., 2011). Nevertheless, the inconsistencies in these findings warrant further exploration of the laterality of internal movement representations.

1.7. Thesis rationale

The research outlined above leads to some important questions that intend to be tackled in this thesis. The work of this thesis focused on two main questions. Firstly, whether apraxia can be

attributed to impaired internal representations of movement due to disruption of the ventro-dorsal stream. Secondly, whether internal representations of movement are reliant on maintained processing within the left inferior parietal lobe (IPL).

In the first empirical study in Chapter 2, a newly devised perceptual task was used. Building on previous research, this initial study assessed whether apraxic patients demonstrated a selective deficit in the perception of how objects are manipulated for use (e.g. how a hammer is held). Further, by including a control condition assessing the integrity of functional semantic representations of how two objects interact in the absence of the actor (e.g. how a hammer hits a nail), this study explored whether motoric and non-motoric action representations are dissociable and if the latter are intact in these patients. If apraxia is attributed to impaired motor imagery due to ventro-dorsal disruption, these patients should perform accurately when making non-motoric functional semantic decisions, whilst manipulation decisions are disrupted. Based on the second aim of this thesis, it is expected that apraxic patients demonstrating a selective impairment in the perception of object-use manipulation will have lesions that disrupt the ventro-dorsal pathway, implicating the left IPL in particular.

Given the crude and variable nature of lesion data, a second empirical study described in Chapter 3 directly assessed the neural correlates of motor imagery by applying transcranial direct current stimulation (tDCS) over inferior parietal regions in healthy participants. During the same perceptual task used with patients in Chapter 2, cathodal-inhibitory or anodal-excitatory stimulation of the left IPL should selectively diminish or improve performance during object manipulation perception depending on the stimulation protocol applied. Such behaviour would support the hypothesis that the left IPL forms the critical juncture where internal movement representations are generated and maintained within the ventro-dorsal stream. Further, maintained functional semantic perception would indicate that this is distinct from manipulation perception and not reliant on inferior parietal regions. Coupled with results from the initial patient study, the results from Study 2 would inform theories regarding the cause of apraxia.

In Chapter 4, an additional patient study explored how impaired internal representations of movement affect action execution. This study aimed to assess whether apraxic errors are not only motoric in nature, but also whether these errors are confined to movements reliant on the integration of perception for action. As a majority of previous research has focused on apraxic patients use of familiar objects, Study 3 explored whether apraxia impacts patients ability to learn skilful manipulation of novel objects. Based on the initial aim of this thesis, if apraxia is associated with impaired perception for action via the ventro-dorsal stream, it is possible that apraxic patients' ability to learn skilful manipulation of new objects is affected. Using a grasping task, a

novel experimental delineation assessed performance differences in apraxic, non-apraxic, and healthy age-matched control participants' when lifting and balancing cylindrical objects of differing weight distribution. Weight distribution was indicated either by a low-level visual affordance cue (object structure), high-level visual affordance cue (coloured 'dot' over the weighted end), or memory-associated cue (colour of the object itself). When given high-level and memory-associated cues of weight distribution, inaccurate grasping by apraxic patients would indicate that these patients failed to incorporate perceptual information from ventral regions into their action plans. Alternatively, appropriate grasping of objects based on structural information (low-level visual affordances) would confirm that the traditional dorsal stream is intact. A selective deficit in conditions where stored representations must be incorporated into action plans with maintained grasping based on low-level affordance information would indicate that errors are confined to skilled movement reliant on ventro-dorsal processing. Moreover, maintained dorsal processing may bias grasp-choice towards low-level visual affordance cues, resulting in central grasp-points regardless of weight distribution across all conditions. These behaviours would suggest that apraxia impacts the ability to learn how to skilfully manipulate new objects.

The final empirical study in Chapter 5 explored the methodology tDCS in more detail. As this technique has been seldom used to assess the cognitive aspects of motor control, the efficacy of modulating motor imagery was considered by exploring the effect of different electrode montages and stimulation protocol on performance. Using classic mental rotation tasks shown to evoke motor and visual imagery depending on task requirements, the effect of inferior parietal tDCS on performance was explored. Based on the proposal that internal movement representations within the ventro-dorsal stream are lateralised to the left IPL, stimulation of this region should alter performance when mentally rotating hands (motor imagery) but not objects (visual imagery). The goal of this study was to inform the second aim of this thesis of whether the left IPL is critical in generating and maintaining internal movement representations. Selective modulation of motor imagery through left IPL stimulation would also support the suggestion that apraxic symptoms are related to impaired processing in the ventro-dorsal pathway.

1.8. Thesis methodology

The studies reported in this thesis are divided into two methods: behavioural research with left hemisphere stroke patients with apraxia, and neuromodulation with healthy populations using transcranial direct current stimulation (tDCS). By using neuropsychological and neuromodulatory methods, the current thesis can directly assess the impact of disruption of particular cortical regions on behaviour. The main advantages and disadvantages of each method will be discussed in relation to neuroimaging techniques.

Functional neuroimaging can be used to indicate which areas of the brain are active during a given task. Depending on the technique used, neuroimaging can be both spatially precise and temporally accurate. For example, functional magnetic resonance imaging (fMRI) is a frequently used non-invasive technique that measures changes in haemodynamic response in the brain during cognitive tasks; increased blood flow in a particular region is interpreted as increased neural activity in response to task demands. Therefore brain regions showing these increases in blood flow are indirectly interpreted as being involved in the particular mental processes being assessed.

Although a direct relationship between haemodynamic changes and the underlying neural response has been confirmed, the biggest limitation of fMRI, or functional neuroimaging in general, is that these methods only provide an indirect suggestion of which brain regions are necessary during a particular task. Causality of brain activity and cognitive function can only be inferred from these techniques. This is particularly evident in the research described in the first part of the general introduction where neuroimaging implicates an array of cortical regions along the visuomotor network that are active during motor imagery. However, lesions to certain regions of the visuomotor network do not always give rise to apraxic symptoms purportedly caused by damage to this imagery process.

Alternatively, neuropsychological and neuromodulatory approaches allow the causal relationship between observed behaviour and brain function to be assessed. Focusing on studies with clinical populations, the role of specific brain regions in particular cognitive functions can be examined by associating deficits in task performance with lesion location. By teasing apart the functions that are maintained and disturbed, clinical populations give enormous insight into the functional role of different brain structures. Patients can be explored as case studies, examining precise lesion location and the resultant selective deficits or by grouping patients with similar behavioural deficits to establish whether there are common regions of damage that may be the cause of these impairments. However, locating and identifying case study patients with very specific lesion location and corresponding behavioural deficits is extremely rare. For example, patient DF who suffers from visual form agnosia due to damage to occipital regions of the ventral stream in 1988 continues to inform current understanding of the two visual pathways model (Milner et al., 1991; Goodale et al., 1994). Equally, recruiting and testing a number of patients with similar deficits is time consuming. Lesions are often extensive and involve a range of cortical areas and underlying white matter, meaning that no two patients are the same. Further, the neural networks compromised may be more widespread, which means it cannot be conclusively demonstrated that the neurons in a specific region of the brain are critical to a cognitive process or whether disruption to that area disconnects information being transferred along a network.

On the basis of findings from neuroimaging and neuropsychology, neuromodulation techniques allow the neural correlates of different cognitive functions to be more precisely targeted. Unlike lesion analyses, neuromodulation can be applied over very specific cortical regions to a large number of healthy participants over several sessions. The effect of stimulation on task performance therefore adds considerable weight to conclusions drawn from other techniques. A frequently used non-invasive technique is transcranial magnetic stimulation (TMS). By producing a rapidly changing magnetic field that passes through the individual's scalp, an electrical current is induced in the brain. Stimulation of the neural tissue causes an action potential, which disrupts the function of the cortical region being targeted (Pascual-Leone, Bartres-Faz, & Keenan, 1999). Disruption of cortical function manifests in observable movement, such as muscle twitches after stimulating the primary motor cortex, or reduced performance in cognitive tasks such as slowed response times. TMS has relatively high spatial and temporal frequency, targeting approximately one centimetre and with single pulse as precise as 70-200 milliseconds. However, TMS cannot be used to assess the function of regions deep in the brain such as subcortical areas.

Another non-invasive neuromodulation technique that has shown potential in recent years is transcranial direct current stimulation (tDCS). tDCS uses a weak direct electrical current to induce changes in cortical excitability. Unlike TMS, it does not induce an action potential in resting neurons, but modulates the spontaneous firing rate of neurons by acting at the level of the membrane potential. By altering a neuron's resting membrane potential, tDCS can cause them to depolarise or hyperpolarise depending on which electrode is stimulating the cortical region. Anodal stimulation increases neuronal excitability, causing increased cell firing. Alternatively, cathodal stimulation causes decreased spontaneous cell firing, reducing neuronal excitability. These changes result in increased or decreased performance for each stimulation type respectively allowing the neural correlates of cognitive functions to be considered (Nitsche et al., 2008; Nitsche & Paulus, 2011). For clarity, these classic modulatory effects will be defined when referring to each electrode: 'cathodal-inhibitory' and 'anodal-excitatory'. With minimum electrode sizes of 25cm², tDCS can assess the relationship between two target cortical sites by using bilateral electrode placement for example, or the role of one target region by placing one electrode over a target cortical area while the other is placed in a reference site that is not important to the given task. Although tDCS is not as spatially or temporally precise as TMS, the key advantages of this technique is that depending on how long the stimulation is applied, tDCS can have lasting after-effects on behaviour (Nitsche & Paulus, 2011; Nitsche et al., 2008). Coupled with its low cost and easy application, these after-effects give it great potential as a neurorehabilitation technique (Sparing & Mottaghy, 2008). Recent research indicates that repeated application of tDCS improves post-stroke motor rehabilitation, reduces symptoms in depression, and improves gait in parkinson's patients (Fregni et al., 2005; Nitsche, Bossio, Fregni,

& Pascual-Leone, 2009; Benniger et al., 2010; Brunoni et al., 2012; Fregni et al., 2014). Therefore, any stimulation effects achieved with this technique in the current thesis will support its potential to aid rehabilitation of object-use errors observed in apraxia.

However there are some important considerations when using tDCS. Firstly, recent evidence suggests that the expected effects of tDCS stimulation may not be reliable. The effects of tDCS on behaviour can vary depending on where the electrodes are placed on the head, or more specifically depending on the direction of current flow (Nitsche et al., 2008; Nitsche & Paulus, 2011). Further, identification of robust anodal-excitatory and cathodal-inhibitory effects have been found when looking at motor functions (for example Stagg et al., 2009) but not during cognitive tasks. A review by Jacobson, Koslowsky, and Lavidor (2012) suggested that excitatory effects were more likely to be achieved during cognitive tasks compared to inhibitory effects. Finally, as tDCS more subtly increases or decreases neuronal excitability (compared to inducing action potentials using TMS), it remains possible that participants can compensate for the modulatory effects of stimulation over time. Taking these factors into account, it is important to assess different electrode montages to establish whether robust effects of tDCS can be achieved in the given task. As this technique has been seldom used in motor cognition, the two studies using tDCS in the current thesis (Study 2 and Study 4) therefore explored different stimulation protocol in greater depth.

Overall the use of neuropsychological and neuromodulatory techniques in this thesis will compliment each other by directly assessing whether apraxic symptoms manifest due to impaired internal movement representations stemming from disruption to the ventro-dorsal stream, and more specifically whether this process is dependent on the integrity of the left IPL. It was intended that these techniques add more insight into the causal links between brain area and function that neuroimaging cannot.

Chapter 2

Study 1: Dissociable perception of object manipulation and functional semantic interactions with objects in apraxia

2.1. Overview

As described in the general introduction, patients with apraxia display object-related errors that appear to be restricted to the perception and execution of the gestures appropriate for using objects. The empirical study in this chapter assessed the possibility that these errors stem from impaired internal movement representations (i.e. motor imagery) due to damage to the ventro-dorsal stream. Using a newly devised perceptual task, a critical distinction was made between skilled motoric object manipulation judgements (e.g. how a hammer is held) and non-motoric functional semantic representations of how two objects interact (e.g. how a hammer hits a nail). Selective disturbance of object manipulation perception in apraxic patients would suggest that apraxia is attributed to impaired internal representations of movement due to disruption to the purported ventro-dorsal stream. Further, lesion data suggests the left IPL is directly and indirectly implicated in these patients suggesting internal movement representations are reliant on the integrity of this region. However, further exploration of the neural correlates of motor imagery is needed.

2.2. Introduction

An appropriate object-use grasp is selected based on stored representations of the object including its identity and typical function, with circumstantial information about the structure and location of the object in the given situation. Recent evidence indicates that integration of known and visible properties may be carried out by the purported ventro-dorsal sub-stream within the visual pathways model, with the left inferior parietal lobe (IPL) being the critical juncture where these properties are combined (Rizzolatti & Matteli, 2003; Binkofski & Buxbaum, 2013; Vingerhoets, 2014).

As described in Chapter 1, this proposed ventro-dorsal stream is critical in skilled action execution and during mental representations of movement necessary for movement perception (Jeannerod, 1994; Kosslyn, Ganis, & Thompson, 2001; Lotze & Cohen, 2006; Rizzolatti & Craighero, 2004; Buxbaum & Kalénine, 2010). Importantly, motor imagery is needed when retrieving postural

requirements related to skilled object-use, prospective judgements about object manipulation, and planning of object-related pantomimes (Buccino et al., 2001; Solodkin, Hlustik, Chen, & Small, 2004; Johnson-Frey et al., 2005; Buxbaum et al., 2006; Creem-Regehr, 2009; Gao, Duan, & Chen, 2011). However few studies have directly explored the relationship between apraxia and motor imagery to confirm whether appropriate object-use is reliant on the integrity of the ventro-dorsal stream. By using a firm experimental approach, the current study teased apart different components of object-use to determine whether apraxics show a selective deficit in object manipulation perception.

Data from neuroimaging and neuropsychological research touching on this issue offers support for apraxia being associated with impaired integration of perception and action due to damage to the ventro-dorsal sub-stream. Neuroimaging studies exploring the neural correlates of object knowledge not only confirm that it is segregated across different cortical regions, but also that activations associated with semantic or action-planning tasks appear highly lateralised to the left hemisphere. More specifically, activation of the left IPL has been found when exploring the motoric elements of object-use (Lewis, 2006; Frey, 2007), in particular when participants are required to imagine or pantomime grasping objects for use (Rumiati et al., 2004; Vingerhoets et al., 2008). Dissociable activations when making decisions about object function (i.e. what an object is used for) and manipulation (i.e. how an object is grasped for use) imply that left IPL activation is specific to motoric aspects of object-use. When matching picture or word pairs of objects based on similar manipulation, more extensive left inferior parietal activations are found compared to inferotemporal regions when matching objects based on similar function (Kellenbach et al., 2003; Boronat et al., 2005; Canessa et al., 2008). These activations indicate that perception of object function is more closely associated with semantic processing in the temporal lobe whereas perception of the gestures associated with object-use are closely related to activity within the motor network, with marked left inferior parietal activation.

Although neuroimaging data correlates motoric elements of object-use with cortical regions heavily associated with the ventro-dorsal stream, it remains uncertain whether apraxia is restricted to selective disruption of skilled movement representations. In order to confirm whether apraxia is attributed to disruption in the integration of perception and action, deficits must be limited to the manipulation of objects for use, whilst each aspect of semantic knowledge, or non-motoric representations of object-use, remain intact.

The few studies that have evaluated object knowledge in apraxia support such an expectation. When exploring apraxic patients understanding of the functional purpose of objects and how they are manipulated for this purpose, a relationship appears to be present between apraxia and

manipulation perception, but not between apraxia and function perception. A study by Buxbaum and Saffran (2002) explored function and manipulation perception using word and picture matching tasks. Patients were required to match objects based on similar function or manipulation in the presence of a “foil” object. In the function condition, patients matched objects similar in purpose, for example, a “stapler”, “cellophane tape” (both fasten things together) and a “pen” (the foil object). In the manipulation condition, patients matched objects that are handled similarly when used, for example: an “eggbeater”, “pencil sharpener” (both require a circular hand motion), and a “hedge clipper” (foil). Results confirmed that compared to non-apraxics, apraxic patients were more impaired on manipulation items, but performed comparatively in the function condition. Myung and colleagues (2010) found similar results using eye-tracking and semantic judgement tasks. When compared to non-apraxic patients, apraxics not only performed worse when explicitly matching objects of similar manipulation, but they also showed more latent fixation on manipulation-related stimuli compared to unrelated objects when the manipulation relationship was not relevant to the task. While these studies have begun to disentangle the elements of object knowledge that are disturbed and maintained in apraxia, it is important to also assess their perception of how an object typically interacts with another object in the absence of the actor (e.g. how a hammer hits a nail) in order to dissociate apraxia from a more general deficit in the understanding of skilled object-use.

Corroborating neuroimaging data, the perception of object function is impaired when the temporal lobe is disrupted. Patients with temporal lobe lesions, as in cases of semantic dementia or herpes encephalitis, display deficits in tests of object recognition and function whilst demonstrating the appropriate action for the same objects (Sirigu, Duhamel, & Poncet, 1991; Buxbaum, Schwartz, & Carew, 1997; Bozeat, Lambon Ralph, Patterson, Gerrard, & Hodges, 2000; Mahon & Caramazza, 2003; Negri, Lunardelli, Gigli, & Rumati, 2007). Further, left IPL stimulation using repetitive transcranial magnetic stimulation (rTMS) slows object manipulation judgements whereas anterior temporal lobe stimulation slows function judgements (Ishibashi et al., 2011). The perception of object function therefore appears to be attributed to more ventral and semantic systems (Hodges, Bozeat, Lambon Ralph, Patterson, & Spatt, 2000). Likewise, visual agnosia patient DF who has damage to occipital regions, cannot describe the shape, size and orientation of visually presented objects, but can accurately grasp objects and insert her hands into slots of varying orientation. These movements however are grossly impaired when a short delay is introduced prior to action execution, suggesting her deficits are attributed to maintained dorsal processing allowing online reach-to-grasp whilst ventral processing is impaired (Milner et al., 1991; Goodale et al., 1994).

The data from these experiments not only suggest that transitive errors in apraxia are strongly related to motoric elements of object-use as opposed to non-motoric representations of objects, but also indicates that manipulation features of skilled object-use remain intact but less accessible for cognitive processing. These selective deficits support the suggestion that apraxic symptoms are strongly related to impaired integration of perception and action necessary to generate internal motor representations for skilled object-use, attributed to the ventro-dorsal sub-stream.

However as described, a common limitation of these studies is that the extent of maintained perception of object function in apraxia remains uncertain. Due to the use of pictures or words of objects in isolation during function decisions, it remains possible that patients may understand the functional *goal* of object-use without a clear idea of the actions required by both the object and the actor to achieve that goal. In order to use an object for a given purpose, an individual must identify the following: i) what the object(s) is used for ii) the functional parts of the objects and the motion required to fulfil that purpose, and iii) how to manipulate the object for use. For example, when using a hammer, an individual must understand i) a hammer is used to apply impact to another object, ii) the head of the hammer must move in a downward motion onto the object being hit, such as a nail, and iii) a power grip must be applied around the handle of the hammer. When presenting an image of the object in isolation, the first two non-motoric aspects of object-use cannot be distinguished. In light of this, apraxia may be attributed to a more general semantic deficit in that patients understand the functional goal of the object in question but not the actions required to achieve that goal. If this were the case, it would be overly simplistic to assume that apraxia is caused by disruption within the ventro-dorsal stream; non-motoric errors in apraxia would suggest that the deficit is not caused by disturbed integration of perceptual information from the ventral pathway into the dorsal action system, which is the purported role of the ventro-dorsal pathway.

Using a series of perceptual matching tasks, the current study aimed to further tease apart the forms of object knowledge maintained in left hemisphere stroke patients with apraxia. By dissecting each aspect of object-use to account for the distinctions outlined above, these findings will confirm more confidently whether apraxia is attributed to impaired integration of perception and action necessary for skilled object-use. Patients were assessed not only on their semantic understanding of objects, but also on non-motoric ‘action representations’ of objects, in other words how an object typically interacts with another object in the absence of the actor (e.g. how a hammer hits a nail), and motoric features, or object manipulation perception, of how the object is handled for use (e.g. how the actor manipulates the hammer to apply impact). The use of a perceptual task allowed a clear-cut distinction to be made between each aspect of object-use maintained in apraxia whilst also enabling both ideational and ideomotor apraxia to be assessed.

As observed in the core symptoms of apraxia, pantomime is more largely affected, as patients cannot rely on the physical properties of the object to afford the appropriate gesture for use (Randerath et al., 2011; Vingerhoets, 2014). If an action execution task were conducted, deficits in object-use would be heavily compensated by reliance on visual affordances.

It is hypothesised that if apraxia reflects deficient access and implementation of motor representations associated with skilled object-use due to impaired integration of perception and action, these patients should perform well when making non-motoric semantic or functional semantic decisions about how objects are used, but show a selective difficulty making perceptual decisions about how objects are manipulated for use. Such behaviour would not only confirm that motoric and non-motoric elements of object-use are perceptually independent but support the proposal that disruption of the ventro-dorsal stream results in apraxia. Patients with these deficits are also expected to have lesions that implicate the left IPL. However if apraxic patients perform poorly when making non-motoric functional semantic and motoric manipulation decisions, this would suggest that apraxia may be associated with a more general deficit in the understanding of skilled object-use that cannot be attributed to impaired integration of perception and action.

2.3. Method

2.3.1. Participants

A total of 39 participants were recruited; 14 acute stroke patients with apraxia ($M_{\text{age}} = 68 \pm 11$, 7 male) and 25 age-matched healthy control participants ($M_{\text{age}} = 70 \pm 8$, 12 male). All participants were formally right-handed and gave informed consent to participate in the study. The study received ethical approval from the local NHS ethics committee and the ethics committee within Northumbria University's Department of Psychology.

Apraxia patients were recruited from National Health Hospitals and rehabilitation centres in the North East of England. Based on CT, MRI scans and clinical notes, patients were selected having suffered a brain haemorrhage or an infarct in the left hemisphere within the last six months. Patients presented with degrees of right-sided weakness, aphasia, or sensory loss. Symptoms of apraxia were determined based on gesture imitation and object-use (pantomime and actual use) tests; patients were recruited if they performed abnormally in one or more of the apraxia screening tools. The full screening battery was given within a few days of experimental testing. See Table 2.1 for patient details and Table 2.3 for details on apraxia screening performance.

Based on clinical notes and additional standard test batteries, patients were excluded if they showed i) any global cognitive deficit or known dementia, ii) severe receptive aphasia or were

unable to follow one-stage commands (based on the token test for language comprehension, De Renzi & Faglioni, 1978), iii) a history of alcohol dependence or evidence of substance abuse, iv) significant visuospatial neglect (based on the Apples Test by Bickerton, Samson, & Humphreys, 2011).

Table 2.1. Description of each apraxic patient in Study 1.

The description includes MS and GW who were excluded due to poor performance on the screening conditions of the experimental task.

Patient	Sex	Age at test (years)	Days post stroke at test	Right sided motor weakness on admission	Aphasia noted on admission	Neglect/ hemianopia	Language comprehension (stage reached of Token Test)	Apraxia Screen performance (%) ^a
FR	M	81	40	Y	N	N	6	96
JAH	M	72	41	Y	N	N	6	93
JH	F	66	35	Y	N	N	6	95
HG	M	81	64	Y	Y	N	6	88
DF	M	68	63	Y	Y	N	6	90
MAS	F	75	20	Y	Y	N	5	85
AA	F	81	19	Y	Y	n.t.	n.t.	58
JA	F	46	61	Y	Y	N	2	83
PB	F	63	51	Y	Y	N	5	67
AH	F	72	61	Y	Y	R neglect	6	88
WM	M	78	62	Y	N	N	6	85
TM	M	61	160	Y	Y	N	6	95
MS	F	60	58	Y	Y	L neglect	4	24
GW	M	49	101	Y	Y	n.t.	3	52

Note. F: Female; M: Male; Y: Yes; N: No; L: Left; R: Right; n.t.: Not Tested

^aApraxia Screen performance (%) is the overall accuracy across all the apraxia screening tests: imitation (hand and finger gestures) and object-use tasks (pantomime and actual use).

Details of each patient's lesion as described in the CT and/or MRI reports can be found in Table 2.2. This table also includes details of the Brodmann areas implicated. To determine which Brodmann areas were damaged, each patient's lesions were mapped onto the digital brain image on the basis of the radiologist's report using MRICron software package (Rorden, Karnath, & Bonilha, 2007; <http://www.mccauslandcenter.sc.edu/mricro/mricron/>). Scans were normalised (using Clinical Tool box software through SPM; Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012; <http://www.mricro.com/clinical-toolbox/>) and applied to the Brodmann Atlas included in MRICron. Figure 1.1 includes scan slices of lesions for each patient.

Healthy control participants were recruited from the Psychology Department's participant database. These participants were age-matched to the apraxic patients and did not have a history of brain damage or stroke. As compensation for their time, participants received £3.

Table 2.2. Description of each patient's lesion in Study 1.

Detailed is each patient's lesion as described in the radiologist's CT and/or MRI reports and when mapped onto the Brodmann atlas.

Patient	Lesion includes IPL	Lesion – left hemisphere lesion information on basis of acute CT/MRI report	Brodmann Areas damaged on basis of clinical scan (% = amount lesioned)		
			>75%	25-75%	<25%
FR	Y	New infarct L posterior horn of internal capsule; old L parieto-occipital lesion	2	40 , 41	4, 21, 39 , 42, 48
JAH	N	L cerebellar infarct			
JH	N	L thalamic bleed			
HG	Y	L parietal infarct			2, 3, 6, 19, 39 , 40 , 48
DF	-	Evolving L fronto-temporo-parietal infarct & L insula			
MAS	N	Small vessel disease affecting periventricular white matter, L temporal lobe, & L internal capsule			
AA	Y	L MCA infarct involving parietal white matter and cortex	42	17, 40 , 41	21, 37, 39
JA	N	L MCA infarct	34, 38	47	6, 11, 20, 21, 22, 41, 44
PB	Y	Large L frontal bleed	3, 4, 6	8	9, 32, 40 , 43, 44, 46
AH	N	L MCA infarct involving L putamen, internal capsule, & caudate head. Extending into L frontal white matter	34		10, 11, 25, 32, 45, 46, 47
WM	-	L total anterior circulation infarct			
TM	N	Ischaemic change in the L MCA occlusion			42

Note. Y: Yes; N: No; L: Left; R: Right; ACA: Anterior Cerebral Artery; MCA: Middle Cerebral Artery.

Brodmann areas attributed to the inferior parietal lobse (areas 39 & 40) are indicated in bold.

Scan reports details only are included for JH and WM because their scans could not be obtained for digitation, for DF because the scan was performed too early for the lesion to be accurately localised, and for JAH because his lesion was confined to the cerebellum. MS and GW do not feature because they were excluded on failing the perceptual screening (for lesion details see the data analysis section of the method).

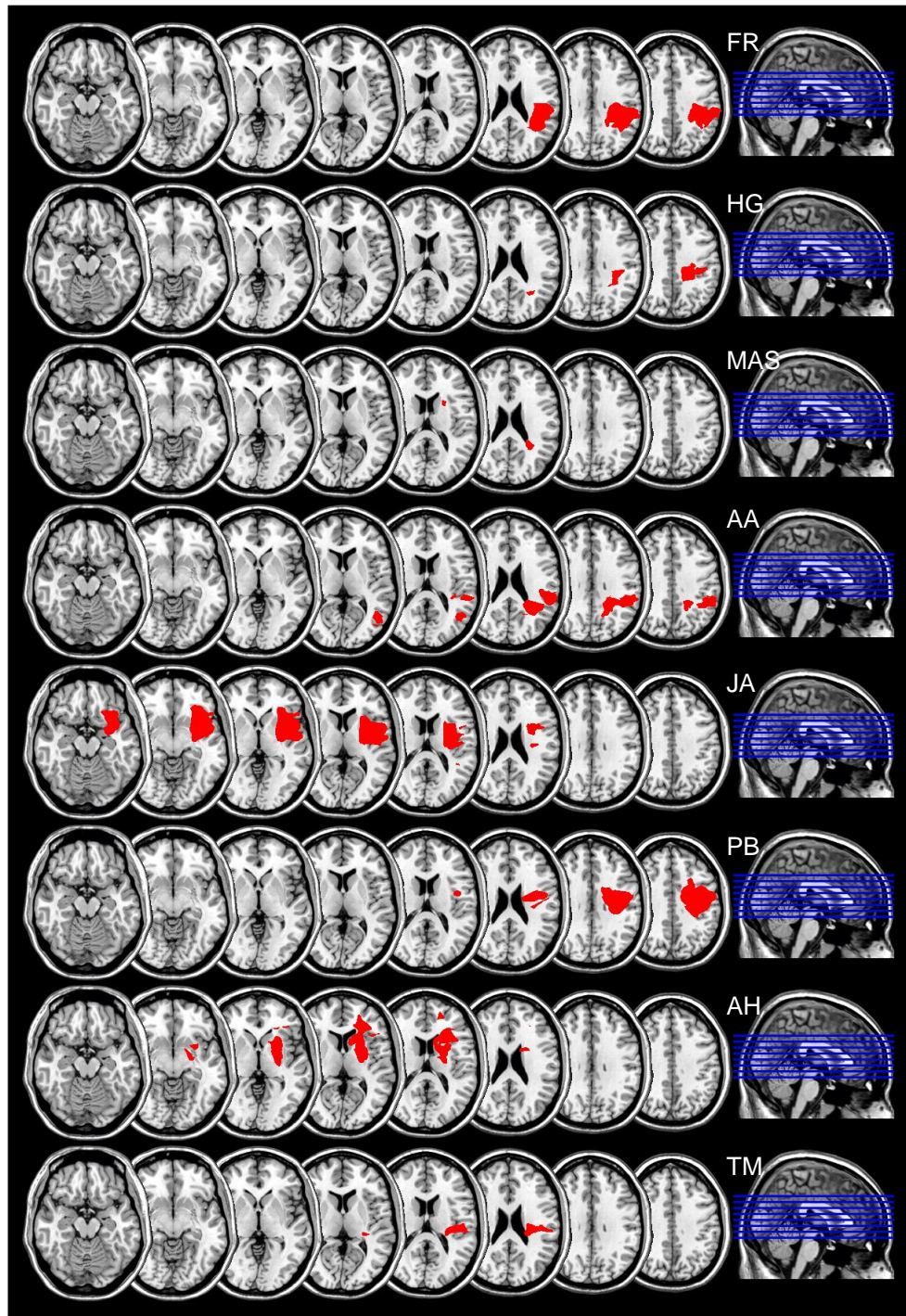


Figure 2.1. Scan slices of lesions of each patient in Study 1.

Scan slices were applied to a template scan allowing clear visualisation of the anatomical landmarks using MRICron software package (Rorden et al., 2007; <http://www.mccauslandcenter.sc.edu/mricro/mricron/>). Clinical scans could not be obtained for patients JH and WM; the scan for DF was performed too early for the lesion to be accurately localised. JAH is not featured as his lesion was confined to the cerebellum. Scans for patients MS and GW are not shown here because they were excluded on failing the perceptual screening (for lesion details see the data analysis section of the method).

Table 2.3. Apraxia screening performance of patients in Study 1.

Screening performance and error types including excluded participants MS and GW.

Patient	Apraxia Screening							
	Gesture Imitation (total score)				Object use (total score)			
	Hand (20)	Errors	Fingers (20)	Errors	Pantomime (53)	Errors	Actual (18)	Errors
FR	20		17	<i>fe</i>	53		18	
JAH	16	<i>hm; sm</i>	20		48	<i>bpo</i>	18	
JH	19		17	<i>fe</i>	53		18	
HG	10	<i>hm; sm</i>	18/18		53		18	
DF	15	<i>hm</i>	19		47	<i>bpo; sm</i>	18	
MAS	17	<i>hm</i>	19		31	<i>bpo; sm</i>	18	
AA	10	<i>hm; sm</i>	12	<i>p of hands; fe.</i>	21	<i>so; ss</i>	15	<i>so; ss</i>
JA	19		20		26	<i>ao; aa; gm; sm</i>	16	<i>ao; aa; gm; sm</i>
PB	17	<i>hm; sm</i>	17	<i>fe</i>	14	<i>so; aa; bpo; ss</i>	13	<i>ao; aa</i>
AH	19		19		33	<i>ao; bpo; sm; ss;</i>	18	
WM	18	<i>sm</i>	12	<i>sm</i>	48		18	
TM	17	<i>fe; sm</i>	19		53		18	
MS	5	<i>p; hm; fe</i>	0	<i>fe; sm</i>	3	<i>ao; bpo; ss</i>	12	<i>ao; so; aa; ss</i>
GW	16	<i>hm; sm</i>	4	<i>p of hands; sm</i>	10	<i>ao; aa</i>	16	<i>aa</i>

Note. Types of performance error have been given the following acronyms: GESTURE IMITATION: perseveration (p); hand misorientation (hm): misorientation of the hand relative to the face; finger extension (fe): incorrect fingers extended from hand; spatial misorientation (sm): hand misorientation relative to the experimenter, e.g. back of hand instead of palm facing. OBJECT USE: action addition (aa): miscellaneous actions not interpretable as a step in the task, e.g. waving; action omission (ao): failed to perform any recognisable action; step omission (so): failed to complete some parts of the movement, e.g. rotating hand when squeezing a lemon; body-part-as-object (bpo): e.g. brush teeth with finger; semantic substitution (ss): e.g. stir with fork; grasp misestimation (gm): incorrect grasp size/type for object, e.g. pincer grip for cup; spatial misestimation (sm): incorrect relationship between object relative to body or another (reference) object.

2.3.2. Procedure

Healthy control participants were tested within the Psychology Department and patients were tested at home or at the bedside over two to three sessions, each session lasting approximately 30 minutes. Initially, patients were screened for cognitive, motor, or sensory deficits before being assessed for symptoms of apraxia. Lastly, patients were given the experimental task. All tasks were presented on paper.

2.3.3. Materials

Apraxia Screening

Imitation of hand and finger postures (Goldenberg, 1996). Patients were required to imitate hand and finger postures demonstrated by the experimenter. Hand postures consisted of different hand positions relative to the head and finger postures defined by configurations of the fingers irrespective of the hands position relative to the body. The experimenter sat opposite the patient and demonstrated each gesture ‘like a mirror’, performing each posture with their right hand to be imitated with the patients’ left hand. Imitation was permitted after the demonstration had ended. Two points were given for successful imitation on the first trial; one point if the patient was successful after a second demonstration; zero points if the patient failed to imitate the posture correctly. Ten gestures of each kind were presented and a total score of 20 could be achieved.

Pantomime of object use (based on Goldenberg et al., 2007). Drawn images of 19 objects taken from Cycowicz, Friedman, Rothstein, and Snodgrass (1997) were presented and patients were asked to demonstrate their use. The examiner named the action and patients were marked on the presence or absence of predefined movement features; a maximum of 53 points could be obtained, with less than 43 points considered pathological. For example, when demonstrating how to “write with a pencil”, patients received three points if they used a “precision” grip, made “movements of small amplitude in the horizontal plane”, and the “grip is close to but does not touch the table”. Body-part-as-object errors were marked as incorrect except when demonstrating the use of scissors.

Actual object use (based on De Renzi & Lucchelli, 1988). 18 of the objects presented in the pantomime test were given to the participant to demonstrate their use. One point was given for every object used correctly, and zero for incorrect movements. It was considered pathological if errors were made when demonstrating the use of two or more objects.

Experimental Task

Across four conditions, participants' object-use perception was assessed. The first two conditions screened semantic object understanding; the third required a functional semantic decision; and fourth an object manipulation decision. The stimuli included drawn pictures of objects taken from Cykowicz et al. (1997) and pictures taken from an Internet search engine and then modified. Hand postures featured were created using a Canon Powershot SX200 IS 12.1 mega pixel camera. Each posture was created by holding the target object, removing it, and maintaining the posture whilst the photograph was taken. The photos were edited and grey scaled using GIMP 2.8 image manipulation program. Two independent assessors confirmed reliability of these photos.

In each condition, participants were given simple verbal instructions and asked to point to the correct image amongst distractors. The same target objects were used across all conditions to directly assess the point at which individuals' object-use perception deteriorated. The distractor images consisted of an 'afforded' distractor, defined as physically plausible but highly unlikely for effective object-use, and 'unafforded' distractor, defined as physically implausible/impossible for object-use. There were 20 trials in each of the four conditions, totalling 80 overall. Accuracy and response times were recorded; participants were given one point for correct trials and zero for incorrect.

Semantic object understanding (screening): The initial *Object Identification* condition required participants to point to the target object amongst three distractors in a 2x2 array. Distractors consisted of random objects; some of which also appeared in upcoming conditions to minimise the number of new stimuli seen by the participant. In the second screening task and subsequent conditions, the target object was presented as a 'pivot' with correct and distractor images presented underneath. The second condition, *Object Pairing* required participants to point to the object typically used with the target. The paired object was presented with two distractors, one affordance-related and one affordance-unrelated. For example, the target 'hammer' could be paired with a 'nail' (correct), 'drum' (affordance-related/incorrect), and 'doorknob' (affordance-unrelated/incorrect).

Functional semantic decision (object-object): Participants were required to identify the scenario in which the target object was being used correctly with the paired object shown in the previous condition. Three 'object-object interaction' images were presented, one correct and two incorrect (affordance-related and affordance-unrelated). The paired object (e.g. the nail when used with the target hammer) maintained the same orientation in all images.

Manipulation decision (hand-object): Participants pointed to the correct hand posture for using the target object. Two postures were presented, one correct and one affordance-related incorrect. Participants were requested not to pantomime the movement. Left-handed postures were presented so that participants were able to imagine the movement with their unaffected hand in the event of right-sided weakness (Figure 2.2 shows an example of each experimental condition).

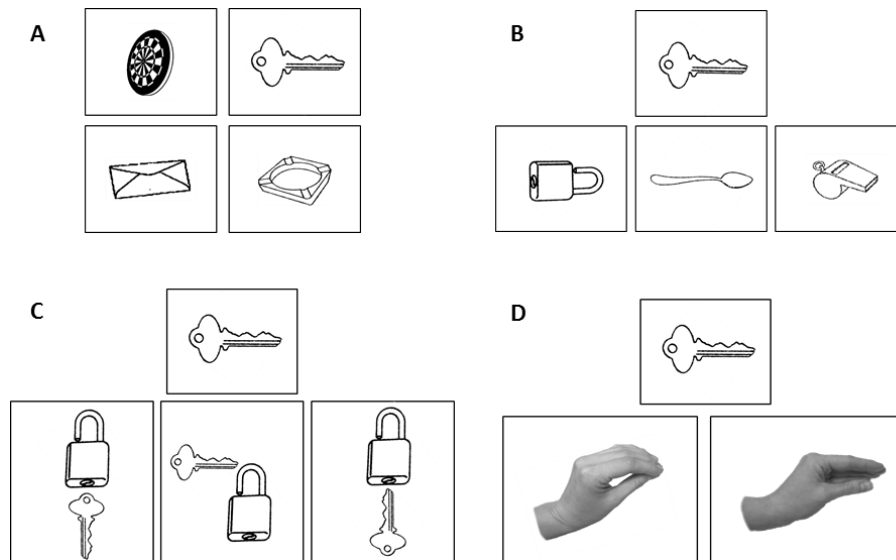


Figure 2.2. Stimuli presentation in each condition of the experimental task in Study 1.

Using a ‘key’ as the example target object: A) & B) screened object understanding with Object Identification and Object Pairing conditions. Respectively, participants pointed to the target object and the object typically used with it. C) Functional Semantic decision assessed perception of object-object interaction; participants indicated how the paired objects are typically used together by selecting the target image (right) from affordance-related (left) and affordance-unrelated (middle) distractors. D) Manipulation decision assessed hand-object perception; how an object is typically held for use between the correct posture (left) and affordance-related incorrect (right).

2.3.4. Data Analysis

Participants were excluded from the study if accuracy was less than 90 percent (less than 18 correct of the 20 trials) in either condition of the Semantic Object Understanding screening, as this suggested a level of semantic deficit. Based on this criterion, patient MS and GW were excluded due to 70 and 85 percent accuracy respectively in the Object Pairing condition. CT and MRI scan reports confirmed MS suffered a left temporal lobe sub-acute infarct (implicating Brodmann areas 2, 3, 4, 8 and 40) whilst GW had infarcts in the left temporo-parietal, basal ganglia, and parieto-occipital regions (Brodmann areas 6, 19, 20, 22, 31, 34, 36-39) consistent with more semantic impairments. The remaining 12 apraxic participants’ performance was equal

to or greater than 95 percent in both conditions of the semantic screening. A one-sample t-test confirmed that performance was comparable to 100 percent accuracy; Object Identification ($M=99.615$, $SD=1.387$), $t_{(12)}=-1.0$, $p=.337$, Object Pairing ($M=98.846$, $SD=2.193$), $t_{(12)}=-1.897$, $p=.082$. Alpha level for significant scores was less than .05.

A mixed model analysis of variance (ANOVA) was conducted to compare performance of apraxic and control participants during the Functional Semantic and Manipulation conditions. A score of accuracy (%) divided by reaction time (RT) in seconds was measured to account for any speed-accuracy trade-off. A more positive score characterises high accuracy and fast RT. Post-hoc analyses were conducted using independent samples t-tests with a Bonferonni correction for multiple comparisons.

Finally, using the data from the apraxic participants alone, the relationship between apraxia severity and task performance was explored using a non-parametric one-tailed Spearman's rho correlation. Apraxia Screen performance was calculated as the overall accuracy (%) across all the apraxia screening tests: imitation (hand and finger gestures) and object-use tasks (pantomime and actual use). A composite score of task performance was calculated: Functional Semantic condition (Accuracy/RT) minus Manipulation condition (Accuracy/RT). If the composite score deviated from zero this indicated a greater difference in performance between conditions; a positive composite score illustrated a poorer performance in the Manipulation condition compared to the Functional Semantic condition and a negative score illustrated a comparably poorer performance in the Functional Semantic condition.

2.4. Results

2.4.1. Functional Semantic and Manipulation Task performance – Apraxic patients versus Healthy controls.

The aim of the study was to confirm whether patients with apraxia are impaired when making perceptual decisions regarding skilled object-use said to rely on ventro-dorsal processing. A mixed model ANOVA was conducted to confirm whether the performance of apraxic patients differed from control participants, and if so, whether these differences were specific to the Manipulation condition. Accuracy/RT performance was explored between Task (Functional Semantic & Manipulation) x Apraxia (Apraxic Patients & Healthy Controls).

An initial main effect of Task ($F_{(1,35)} = 55.440$, $p < .001$) indicated that performance in the Manipulation condition was poorer overall ($M = 1.271$, $SD = .242$) compared to the Functional

Semantic condition ($M = 1.533$, $SD = .164$) across participants. Further, a significant main effect of Apraxia ($F_{(1,35)} = 10.369$, $p = .003$) confirmed that apraxic patients performed worse ($M = 1.309$, $SD = .272$) than controls ($M = 1.495$, $SD = .133$) in both task conditions.

Of interest, the significant interaction Task x Apraxia ($F_{(1,35)} = 7.367$, $p = .010$) revealed that performance differed between each participant group and task condition (see Figure 2.3). Post-hoc independent samples t-tests confirmed that apraxic patients performed significantly worse ($M = 1.131$, $SD = .320$) than controls ($M = 1.412$, $SD = .164$) during the Manipulation condition ($t_{(13.841)} = -2.863$, $p = .013$). Alternatively, performance was comparable between apraxic and control participants during the Functional Semantic condition ($t_{(13.255)} = -1.321$, $p = .209$).

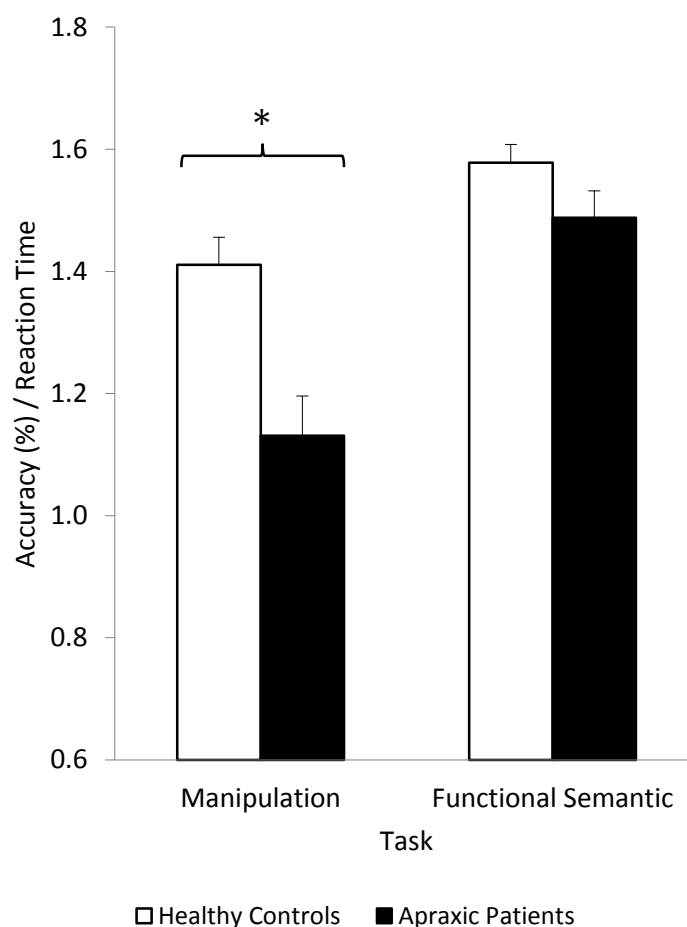


Figure 2.3. Performance of apraxic and healthy participants in Study 1.

Accuracy(%) / Reaction Time is presented for the Functional Semantic and Manipulation conditions of the experimental task. A high score represents high accuracy and fast reaction time (RT). Standard Error (SE) bars are plotted for each condition and participant group. An asterisk marks the significant difference between apraxic and control participants in the Manipulation condition ($p < .05$).

2.4.2. Apraxia Severity

The relationship between apraxia severity and task performance was explored using a non-parametric one-tailed Spearman's rho correlation. It was anticipated that increase in apraxia severity would correlate with a decrease in performance in the Manipulation condition. A significant negative correlation between performance on the apraxia screening and the composite score ($r_{s(12)} = -.522, p = .041$) was confirmed. Observing the scatterplot in Figure 2.4, there appears to be a linear trend in composite performance and apraxia screen performance, with performance in the *Manipulation* task decreasing as apraxia severity increases.

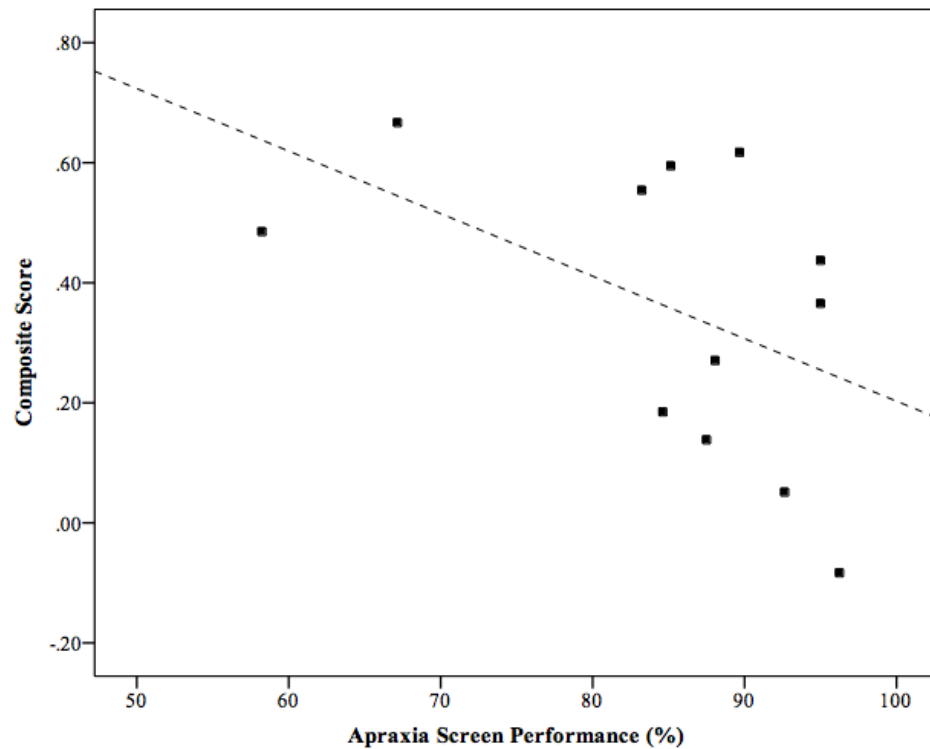


Figure 2.4. Correlation scatterplot between composite score and apraxia screen in Study 1.

Scatterplot of the correlation between composite score of Accuracy(%)/RT for Functional Semantic minus Manipulation conditions and apraxia screen performance (%). A dashed line of fit is plotted, $R^2 = .242$. The greater the composite score deviated from zero the greater the difference in performance between the Functional Semantic and Manipulation conditions; a positive composite score indicated a comparably poorer performance in the latter condition and a negative composite score indicated a comparably poorer performance in the former. A high percentage indicated accurate performance in apraxia screening.

2.5. Discussion

To confirm whether apraxia is associated with impaired internal movement representations due to ventro-dorsal damage, it was important to assess whether apraxic patients had impaired perception of motoric elements of object-use (object manipulation) with maintained non-motoric ‘action representations’ of how an object typically interacts with another object in the absence of the actor (functional semantic perception). Previous studies have overlooked this distinction. By documenting each patient’s lesion and dissociable impairments in these tasks, Study 1 also aimed to confirm whether integration of perception and action via the ventro-dorsal stream is reliant on preserved processing in the left IPL.

When comparing apraxic performance to healthy controls, apraxic patients made considerably more errors perceiving motoric hand-object interactions in the Manipulation condition compared to control participants. This is consistent with previous research illustrating that apraxic patients make errors when imagining or pantomiming object-use, or when matching objects based on similar manipulation (such as a computer keyboard and piano) (Goldenberg, 1995; Buxbaum & Saffran, 2002; Daprati & Sirigu, 2006; Myung et al., 2010). Alternatively, apraxic patients performance in the Functional Semantic condition was comparable to controls, demonstrating maintained perception of non-motoric object-object interaction. Coupled with accurate performance in the semantic screening tasks, these results support the proposal that non-motoric features of object-use, including ‘action representations’ of how objects interact with each other, are not associated with apraxia. By maintaining the same target objects throughout each experimental condition, accurate performance in the semantic screening tasks confirmed that any errors in later conditions could not be attributed to impaired semantic representations. These findings support previous research indicating that apraxic patients have maintained ventral processing and can appropriately match objects of a similar function (Buxbaum & Saffran, 2002; Myung et al., 2010).

The negative correlation between apraxia screen performance and composite score emphasises the relationship between apraxia and motor representations of object-use; as severity of apraxic symptoms increased, performance in the Manipulation condition decreased compared to the Functional Semantic condition. Although a causal link cannot be verified through correlation, coupled with the dissociable performance between apraxics and healthy controls, the current data strongly suggests that deficits seen in apraxia are associated with impaired perception of motoric features of object-use. This adds weight to the suggestion that apraxia is associated with impaired internal movement representations.

Another goal of the current study was to confirm whether the left IPL is the critical juncture where perceptual and action processes are integrated via the purported ventro-dorsal sub-stream, allowing accurate manipulation perception. If this is the case, patients with lesions implicating the left IPL were expected to perform poorly in the object manipulation condition. Observing the lesion data from radiologist's reports and digital scans, the lesioned areas in apraxic patients appear to involve the left IPL either directly or indirectly. Approximately half of the apraxic patients had lesions encompassing the left IPL. In the remaining apraxic patients, lesions did not involve the left IPL itself, but were in other regions of the frontoparietal network including the cerebellum, thalamus, broca's area, and underlying white matter, that are heavily associated with disruption of left IPL function, apraxia and object-use deficits (Goldenberg & Hagmann, 1998; Johnson-Frey, 2004; Buxbaum et al., 2005; Buxbaum et al., 2007; Sunderland et al., 2011). A review of apraxia from subcortical damage found that of 82 cases, a majority of patients had lesions implicating the putamen, thalamus, basal ganglia, internal capsule, and periventricular and peristriatal white matter (Pramstaller & Marsden, 1996). In cases where white matter damage disrupts corticocortical and corticosubcortical connections, apraxia can be persistent and severe (Leiguarda, 2001). A review by Lewis (2006) also confirmed that a majority of these regions are part of the cortical network activated during imagined object-use. Therefore, errors in the perception of object manipulation can occur after damage external to left IPL, suggesting that the ventro-dorsal stream can be indirectly disturbed by disrupting communication at different parts of the pathway. These findings support previous research confirming that lesions implicating the left IPL can give rise to apraxia and result in impaired perception of object-use manipulation (Buxbaum et al., 2005; Daprati & Sirigu, 2006; Buxbaum et al., 2007; Goldenberg 2009; Ishibashi et al., 2011). Despite this, the proposal that the left IPL is the critical juncture where perception and action are integrated cannot be confirmed or refuted and therefore warrants further investigation.

In order to dissociate apraxia from a more general deficit in the understanding of skilled object-use, it was necessary to explore patients' perception of the *action* associated with object-use in the absence of the actor. In other words, if apraxic patients are unimpaired in their perception of how the functional parts of each object *interacts* (e.g. how the flame of a match is used to light a candle) and these patients understand the functional goal of the object by appropriately matching objects of a similar function (e.g. a match and a lighter both make a flame), it can be asserted that apraxic impairments lie in the integration of perception and action. By exploring performance when making functional semantic decisions of object-object interactions, the current study confirms more definitively than previous research that apraxic impairments cannot be attributed to a more general deficit in the understanding of skilled object-use existant outside of the integration of perception and action.

The presence of visually afforded distractor stimuli confirms that accurate performance in the Functional Semantic condition was attributed to maintained understanding of object-use; the correct decision was not made by ‘process of elimination’, by choosing the image that looked most plausible based on the physical properties of the objects. As apraxic patients can infer use of objects based on their physical attributes and show marked improvement when actually using objects, particularly in the appropriate context (Goldenberg & Hagmann, 1998; Frey, 2007; Randernath et al., 2011; Vingerhoets, 2014), it was important that task performance could not be attributed to reliance on physical properties that afford object-use as opposed to maintained understanding.

Similarly, when generating stimuli for the Object Manipulation condition, it was critical to ensure the distractor hand gestures did not look appropriate for use whilst not being unafforded to the object itself. If either instances occurred, differences in participant accuracy would reflect inappropriate stimuli; the distractor gesture would look equally plausible as the correct gesture or grossly unafforded for object-use, allowing the correct answer to be reached by spatial rather than motoric processes. Taking this into account, consensus between independent assessors during piloting and accurate performance by healthy participants confirms that the stimuli could be distinguished as correct and incorrect. Likewise, the particularly poor performance by apraxic patients in this condition indicates that the task could not be solved by relying on visual affordances.

Overall, the findings of the present study strongly support the proposal that apraxia reflects deficient access and implementation of motor representations associated with skilled object-use. Maintained performance when making perceptual decisions regarding non-motoric action representations of objects (i.e. object-object interactions) and marked deficits during motoric, object manipulation, decisions suggests that impairments occur when perception and action information must be integrated. Coupled with decreasing performance accuracy with increasing severity of apraxia, it is probable that an additional ventro-dorsal sub-stream exists within the visual pathways model that is critical in this integrative process. However, although lesions appear to involve the left IPL either directly or indirectly, the role of this region in the integration of perception and action needs additional exploration.

Chapter 3

Study 2: Isolated disruption of object manipulation perception using left parietal tDCS

3.1. Overview

The results from Study 1 indicate that apraxia selectively disturbs object manipulation perception whilst functional semantic perception is unaffected. These selective deficits support the existence of a purported ventro-dorsal stream within the visual pathways model that combines known and visible properties of objects necessary for appropriate skilled object manipulation. Examining the lesions of these patients, half had damage directly implicating the left IPL whilst half had lesions that may indirectly impact processing in this region. During the same perceptual matching task used in the previous study with apraxic patients, the current empirical study directly explored the role of the left IPL in representing the manipulation features of object-use using the relatively novel neuromodulation technique transcranial direct current stimulation (tDCS). Results from Study 2 indicate a causal relationship between the left IPL and internal movement representations supporting its role as the critical juncture where known and visible object properties are integrated (Rizzolatti & Matteli, 2003; Binkofski & Buxbaum, 2013; Vingerhoets, 2014).

3.2. Introduction

Consistent activation of the left IPL during motor imagery suggests its essential role in the perception of movement (Rizzolatti & Craighero, 2004; Buxbaum & Kalénine, 2010). Such imagery is necessary when retrieving postural requirements or making prospective judgements about skilled object manipulation (Buccino et al., 2001; Solodkin et al., 2004; Johnson-Frey et al., 2005; Buxbaum et al., 2006; Creem-Regehr, 2009; Gao et al., 2011).

Neuroimaging studies exploring the neural correlates of object knowledge indicates that the left IPL is consistently activated during motoric elements of object-use (Rumiati et al., 2004; Lewis, 2006; Frey, 2007; Vingerhoets et al., 2008). Examining the role of the left IPL in the perception of object-related action, neuroimaging data dissociating representations of object function and manipulation confirms the region is selectively activated in the latter condition (Kellenbach et al., 2003; Buxbaum et al., 2006; Canessa et al., 2008). For example, using fMRI Boronat and colleagues (2005) confirmed that when participants judged whether word or picture-pairs of

objects had the same function (for example a matchstick and a lighter) or manipulation (a piano and a computer keyboard), greater left IPL activation was found bordering the intraparietal sulcus for manipulation-relevant judgements. Functional decisions on the other hand have shown more temporal activation (Kellenbach et al., 2003; Buxbaum et al., 2006; Canessa et al., 2008; Chen, Garcea, & Mahon, 2015). Support for the central role of the left IPL in the simulation of motor aspects of object-use also stems from its consistent activation when participants are required to observe, imagine, or pantomime object-use (Chao & Martin, 2000; Mozaz, Rothi, Anderson, Crucian, & Heilman, 2002; Rumiati et al., 2004; Frey, 2007; Vingerhoets, 2008; Króliczak & Frey, 2009; Vingerhoets, Acke, Vandemaele, & Achten, 2009; Caspers et al., 2010) indicating that the left IPL is central to the simulation of motor aspects of object-use.

As described in Chapter 2, akin to the dissociations found in neuroimaging data when assessing object function and object manipulation, apraxia appears to be associated with deficits in manipulation judgements but not function judgements (Buxbaum & Saffran, 2002; Rumiati et al., 2004; Vingerhoets et al., 2008; Myung et al., 2010). Results from Study 1 offer substantial support for the proposal that apraxia is attributed to impaired internal movement representations due to damage to the ventro-dorsal stream; errors in object-use perception were present when apraxic patients made manipulation judgements whilst performance was appropriate when making functional semantic judgements. However, lesions of the apraxic patients in Study 1 did not always encompass the left IPL, but involved other regions along the frontoparietal network including the cerebellum, thalamas, broca's area, and underlying white matter. In these cases it is possible that communication is being disrupted at different parts of the ventro-dorsal stream by damaging corticocortical and corticosubcortical connections, however this is not certain (Leiguarda, 2001; Lewis 2006).

Using a modified version of the perceptual matching task used in Study 1, the neural correlates of object-use perception were explored directly by applying tDCS to the left IPL of healthy participants. TDCS is a relatively novel neuromodulation technique that involves the application of a weak electrical current onto the scalp through a pair of electrodes (the positive anode and the negative cathode electrode) to modulate cortical function by inducing prolonged, reversible, shifts in cortical excitability. Unlike TMS, tDCS does not induce neuronal action potentials but modifies spontaneous neuronal excitability by depolarising or hyperpolarising the resting membrane potential (Nitsche et al., 2008). Classic assumptions regarding the polarity effects of tDCS indicates that cathodal stimulation inhibits neuronal excitability whereas anodal stimulation enhances neuronal excitability. For clarity, these classic modulatory effects will be defined when referring to each electrode: 'cathodal-inhibitory' and 'anodal-excitatory' (for a more detailed description of tDCS, see the methodology section of the general introduction in Chapter 1).

However, the polarity effects of the cathode and anode are grossly dependent on the stimulation protocol being used; stimulation effects can vary depending on electrode size, intensity and duration of stimulation. Although cathodal-inhibitory stimulation consistently modulates the motor cortex, it has been proposed that anodal-excitatory stimulation over the target site is more likely to modulate performance during cognitive tasks (Nitsche & Paulus, 2011; Jacobson et al., 2012). These findings emphasise the need to explore different stimulation protocol to obtain modulatory effects of tDCS.

Over two experiments with different participants, either cathodal-inhibitory tDCS was applied over the left parietal cortex (approximately over the IPL) with anodal-excitatory stimulation over the contralateral supraorbital ridge (Experiment 1) or anodal-excitatory left parietal and cathodal-inhibitory contralateral supraorbital ridge stimulation (Experiment 2) was applied. It was hypothesised that if the left IPL of the ventro-dorsal stream were critical in the integration of perception and action important for the retrieval of postural requirements for object-use, cathodal-inhibitory stimulation of the left parietal cortex would reduce task performance when making manipulation judgements whereas anodal-excitatory stimulation would enhance performance in this task. Stimulation of the left parietal cortex however would not affect task performance when making functional semantic decisions. In combination with the results from Study 1, these results would confirm more confidently whether apraxia is attributed to impaired ventro-dorsal processing, and whether these representations are reliant on the integrity of the left IPL.

3.3. Method

3.3.1. Design

Two experiments were completed with different stimulation protocol. For each experiment, a within-subject repeated-measures design was used with three independent variables: Task (functional semantic/manipulation) and Stimulation (left parietal tDCS/sham) and Stimulation Block (1/2). The dependent variables measured were response reaction times (RT) and response accuracy (%).

3.3.2. Participants

An opportunity sample of healthy participants was recruited; all participants were right handed (in accordance with the revised Edinburgh Handedness Inventory, Oldfield 1971; Cohen, 2008), received a health screening questionnaire based on Rossi, Hallett, Rossini, & Pascual-Leone (2011) to confirm their eligibility for tDCS stimulation, and gave informed consent. Monetary compensation or course points were offered for their time. For the cathodal-inhibitory study protocol (Experiment 1) 24 participants ($M_{age} 22 \pm 7$, 19 female, laterality quotient 82.50) were

recruited. For the anodal-excitatory study protocol (Experiment 2) a further 23 participants (M_{age} 23 ± 10 , 12 female, laterality quotient 78.12) were recruited.

3.3.3. Transcranial direct current stimulation (tDCS)

A constant direct current was applied during both tasks using a battery driven stimulator (neuroConn, Germany). Two rubber electrodes were inserted into separate sponge pouches that were soaked in saline solution. A lycra cap was placed on the participants head to keep the electrodes in place and a 1.5mA current was applied through a 25cm² electrode over the target site and 100cm² electrode over the reference site. Stimulation was ramped up for 10 seconds and remained online throughout the experimental tasks in accordance with current safety limits for healthy volunteers (Nitsche et al., 2003): experiment one, average stimulation duration 11 minutes ± 2 and experiment two an average of 11 minutes ± 1 , at a maximum current density of 0.06mA (1.5 mA/25 cm²). During the sham condition, stimulation was applied for 30 seconds before being switched off.

Based on the international 10/20 system for electrode placement, the target electrode was placed over the left parietal cortex, approximately over the left IPL; the centre of the electrode was positioned between P3 and CP3 (Harris and Minuissi, 2003) and the reference electrode was placed over the contralateral supraorbital ridge. In experiment one, cathodal-inhibitory stimulation was applied to the left parietal cortex (target) with anodal-excitatory stimulation using the large ‘diffuse’ electrode applied to the reference site. In experiment two, anodal-excitatory stimulation was applied to the left parietal cortex and cathodal-inhibitory stimulation to the reference site. Both experiments consisted of two testing sessions where either real or sham stimulation was applied.

3.3.4. Stimuli

Participants completed the functional semantic and object manipulation tasks used in Study 1, however these were altered to suit computer presentation and extended to include more trials (see Figure 3.1). The experiment was run on a 19-inch computer monitor (1280 x 1024 pixels) and programmed using E-Prime. The centre of the screen was at eye level at a viewing distance of 63cm, which was maintained using a chin rest. Stimulus reliability was evaluated by two independent assessors and based on pilot data from six participants (average accuracy of 94% \pm 10). Stimuli were changed if the average accuracy fell below 75%.

Functional Semantic task. Comprised of drawn pictures of objects taken from the stimulus set by Cykowicz et al. (1997) or modified from an internet search engine. Following a central fixation cross, participants saw one drawn image of an ‘object-object interaction’ and were required to

identify whether the target object was being used correctly with the paired object. Interactions were presented equally in orientations for left- or right-handed use.

Manipulation task. Stimuli consisted of target objects taken from the Bank of Standardized Stimuli (BOSS) (Brodeur, Dionne-Dostie, Montreuil, & Lepahe, 2010) or modified images from an internet search engine. After the central fixation cross, the target object was displayed for 500ms before being replaced by a correct or incorrect hand posture. Participants identified whether the hand posture displayed was appropriate to use the object presented previously. The target object was presented in a non-functional orientation whereas the hand posture was oriented appropriately for object-use. This prevented participants simply matching the images. Participants saw both left and right hand postures for each target object.

3.3.5. Procedure

An initial practice block was completed prior to stimulation enabling participants to reach optimum performance. For respective Functional Semantic and Manipulation tasks, this consisted of 33 and 38 trials. After practice, five minutes of stimulation was applied prior to task onset to ensure stimulation effects were being experienced. Participants then repeated each task whilst stimulation was on going. During stimulation, 66 trials of the Functional Semantic task and 89 trials of the Manipulation task were presented. Each task was split into two main test blocks consisting of 33 trials per block for the Functional Semantic task and 45 and 44 trials in Block 1 and 2 for the Manipulation task. Over two testing sessions, 132 and 178 trials were completed for each task respectively.

Across each task, participants were required to respond as quickly and accurately as possible when deciding whether the functional relationship between the objects or hand postures presented were correct or incorrect for use. Responses were given on a keypad: participants responded 'correct' by pressing number '1' with their left index finger and 'incorrect' by pressing number '3' with their right index finger. Stimulation was switched off after the final task was completed. To avoid response priming for subsequent images, participants did not see both the correct and incorrect image for each target object in one session. In addition to counterbalancing the presentation of correct or incorrect images, task order and stimulation protocol were counterbalanced across participants.

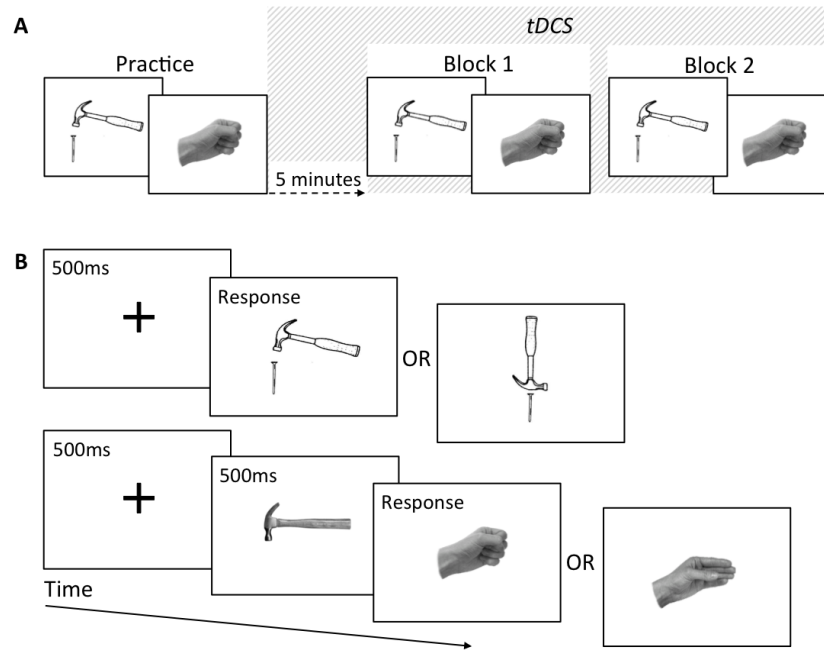


Figure 3.1. Experimental procedure and stimuli presentation for Study 2.

(A) Schematic of the experimental procedure. Note the diagonal striped box depicts the period of tDCS stimulation. (B) Schematic of the stimulus presentation for the Functional Semantic task (top) and the Manipulation task (bottom). The correct stimulus is presented on the left and the incorrect affordance stimulus on the right.

3.3.6. Data Analysis

Reaction times (RT) in milliseconds for correct trials and response accuracy (%) were analysed separately in three-way repeated-measures analyses of variance (ANOVA) for each experiment. Specifically, performance was compared between each Task (Functional Semantic and Manipulation), and Stimulation condition (real stimulation and sham). Unlike more conventional paradigms, where the effects of tDCS are explored after stimulation, the current study explored performance changes during stimulation. This was done to ensure the effects of stimulation were evident, as little is known about the duration of after-effects of tDCS over these densely connected parietal lobes. The effect of tDCS over time was analysed by measuring performance differences across stimulation Blocks (1 and 2), as it was uncertain whether stimulation effects were stable due to so few parietal tDCS perception studies being conducted with continuous stimulation. Further, tDCS effects are state dependent and can change when the brain regions being stimulated are active (Silvanto, Muggleton, & Walsh, 2008; Walsh, 2013). Significant scores were those below the alpha level .05. All participants were included in the final analyses, with average performance $85\% \pm 7$ in Experiment 1, and $85\% \pm 6$ in Experiment 2. RTs greater than three standard deviations from the mean were excluded.

3.4. Results

Study 2 aimed to extend findings from Study 1 with apraxic patients by confirming whether neuromodulation of the left IPL would selectively affect object manipulation perception, as observed in patients with apraxia. This would not only confirm the importance of the left IPL during the perception of motor elements of object-use, but also indicate that dysfunction of this region can impair the perception of these motoric elements. Three-way repeated-measures analyses of variance (ANOVA) examined the effects of Task (Functional Semantic/Manipulation) x Stimulation (left IPL cathode-inhibitory & right supraorbital ridge anode-excitatory/sham) x Stimulation Block (1/2) on response RTs (ms) and response accuracy (%) during stimulation.

3.4.1. Cathodal-inhibitory stimulation of the left IPL.

Reaction Time (ms). The initial three-way ANOVA confirmed a significant interaction Task x Stimulation x Block ($F_{(1,23)} = 4.906, p = .037, \eta_p^2 = .176$). A non-significant main effect of Stimulation ($F_{(1,23)} = .531, p = .473, \eta_p^2 = .023$) and interactions Task x Stimulation ($F_{(1,23)} = 1.139, p = .297, \eta_p^2 = .047$) and Stimulation x Block (Stimulation x Block $F_{(1,23)} = .941, p = .342, \eta_p^2 = .039$) were found. Remaining analyses showed a significant main effect of Task ($F_{(1,23)} = 10.868, p = .003, \eta_p^2 = .321$); RTs were faster in the Functional Semantic task ($M = 1033.060 \pm 245.130$) compared to the Manipulation task ($M = 1157.915 \pm 358.982$). A non-significant main effect of Block ($F_{(1,23)} = 2.600, p = .121, \eta_p^2 = .102$) and significant interaction Task x Block ($F_{(1,23)} = 5.598, p = .027, \eta_p^2 = .196$) were also found. The latter interaction was not explored, as it was not directly relevant to the hypotheses. As the hypotheses concerned the effect of stimulation on performance, post hoc analyses of the three-way interaction were explored using two-way ANOVAs for Task x Stimulation and Stimulation x Block.

As the effect of stimulation appears to present itself differently in the two blocks, this was further explored through separate two-way ANOVAs. Two-way ANOVAs Task x Stimulation for each Block separately revealed a significant interaction of Task x Stimulation for Block 1 (Task x Stimulation: $F_{(1,23)} = 4.692, p = .041, \eta_p^2 = .169$) but not for Block 2 (Task x Stimulation, $F_{(1,23)} = 1.378, p = .253, \eta_p^2 = .057$), suggesting that the effect of stimulation is found in the first block. That the stimulation effects were present in the experimental Manipulation task was revealed by two-way ANOVAs Stimulation x Block for each of the tasks separately showing a significant Stimulation x Block interaction for the Manipulation task ($F_{(1,23)} = 5.481, p = .028, \eta_p^2 = .192$), but not for the Functional Semantic task ($F_{(1,23)} = 1.835, p = .189, \eta_p^2 = .074$). The means show that participants were slower on the Manipulation task when stimulation was applied ($M = 1217.340 \pm 419.111$) compared to sham ($M = 1114.442 \pm 302.334$). The graph on the left of Figure 2.2 demonstrates these task specific effects of inhibitory stimulation on Manipulation task

performance in Block 1. Post-hoc paired-samples t-tests were used to explore the differences between cathodal-inhibitory stimulation (black bars in Figure 2.2) and sham (white bars in Figure 2.2) for each of the blocks and task conditions. The difference between stimulation and sham in Block 1 of the Manipulation condition was expressed in a trend in the post-hoc analysis ($t_{(23)} = 1.869$, $p = .074$), while all other all other post-hoc comparisons were firmly non-significant (Functional Semantic stimulation vs. sham: $p \geq .721$). It appears that stimulation may be slowing performance during the first test block of the Manipulation task only.

Accuracy (%). Stimulation was not found to have an effect on task accuracy: Stimulation, $F_{(1,23)} = .071$, $p = .792$, $\eta_p^2 = .003$; Task x Stimulation, $F_{(1,23)} = .447$, $p = .510$, $\eta_p^2 = .019$; Stimulation x Block, $F_{(1,23)} = .035$, $p = .853$, $\eta_p^2 = .002$; Task x Stimulation x Block, $F_{(1,23)} = .035$, $p = .853$, $\eta_p^2 = .002$. A main effect of Task ($F_{(1,23)} = 76.489$, $p < .001$, $\eta_p^2 = .769$) confirmed that participants were more accurate when making Functional Semantic decisions ($M = 90\% \pm 5$) compared to Manipulation decisions ($M = 81\% \pm 7$). Accuracy was higher in Block 1 ($M = 87\% \pm 6$) compared to Block 2 ($M = 84\% \pm 7$) confirmed by a significant main effect of Block ($F_{(1,23)} = 22.900$, $p < .001$, $\eta_p^2 = .499$). A significant interaction Task x Block ($F_{(1,23)} = 12.441$, $p = .002$, $\eta_p^2 = .351$) was found but not explored.

3.4.2. Anodal-excitatory stimulation of the left IPL

Reaction Time (ms). Opposed to Experiment 1, the three-way ANOVA exploring the effect of anodal-excitatory left IPL stimulation compared to sham on task performance did not find a significant interaction Task x Stimulation x Block ($F_{(1,22)} = 2.347$, $p = .140$, $\eta_p^2 = .096$). Non-significant results were also found for Stimulation ($F_{(1,22)} = .812$, $p = .377$, $\eta_p^2 = .036$), Task x Stimulation ($F_{(1,22)} = .029$, $p = .867$, $\eta_p^2 = .001$), and Stimulation x Block ($F_{(1,22)} = .003$, $p = .958$, $\eta_p^2 < .001$). The main effects of Task ($F_{(1,22)} = 1.809$, $p = .192$, $\eta_p^2 = .076$) and Block ($F_{(1,22)} = 2.155$, $p = .156$, $\eta_p^2 = .089$) were also non-significant. The interaction Task x Block however was significant ($F_{(1,22)} = 10.675$, $p = .004$, $\eta_p^2 = .327$), but was not pursued as it was not directly relevant to the hypotheses. These data suggest that RTs were not in any way affected by anodal-excitatory stimulation.

Accuracy (%). Results reveal non-significant effects of stimulation on task accuracy: Stimulation, $F_{(1,22)} = .052$, $p = .821$, $\eta_p^2 = .002$; Task x Stimulation, $F_{(1,22)} = .021$, $p = .886$, $\eta_p^2 = .001$; Stimulation x Block, $F_{(1,22)} = .253$, $p = .620$, $\eta_p^2 = .011$; Task x Stimulation x Block, $F_{(1,22)} = .485$, $p = .494$, $\eta_p^2 = .022$. A significant main effect of Task ($F_{(1,22)} = 57.400$, $p < .001$, $\eta_p^2 = .723$) confirmed that accuracy was greater in the Functional Semantic task ($M = 90\% \pm 5$) compared to the Manipulation task ($M = 80\% \pm 9$). Main effect of Block ($F_{(1,22)} = 57.629$, $p < .001$, $\eta_p^2 = .724$) indicated that accuracy was greater in Block 1 ($M = 89\% \pm 7$) compared to Block 2 ($M = 83\% \pm$

8). Finally a significant Task x Block interaction ($F_{(1,22)} = 6.680, p = .017, \eta_p^2 = .233$) was found but not explored.

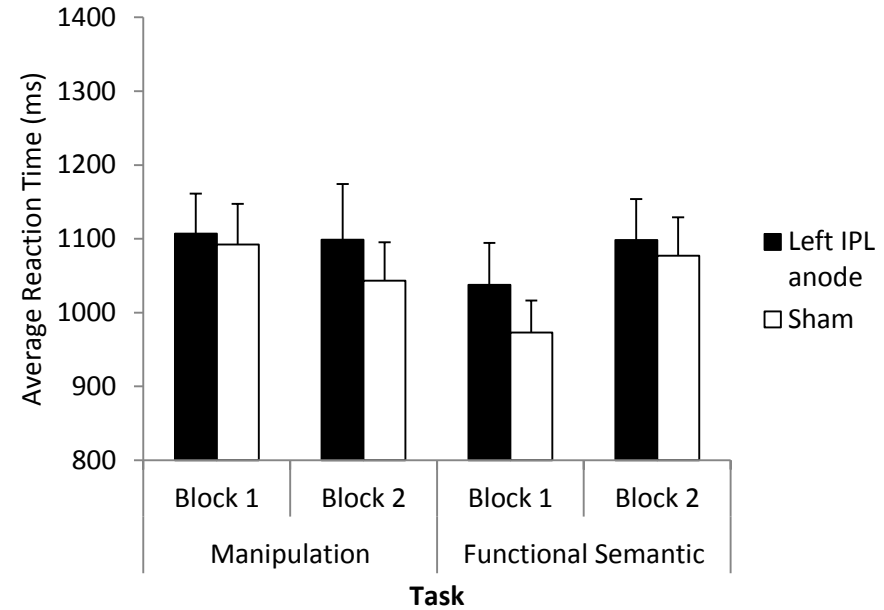
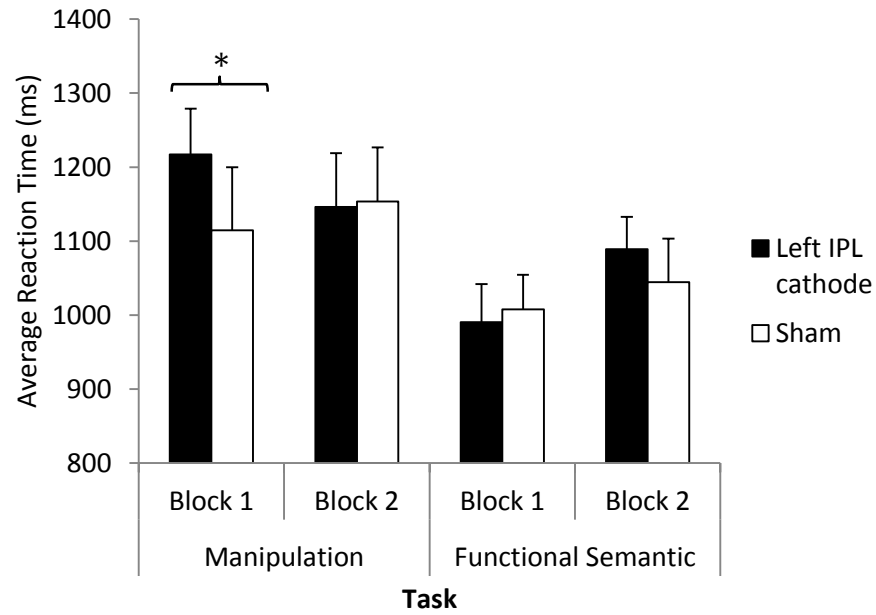


Figure 3.2. Reaction times for Experiment 1 and 2 in Study 2.

Average reaction times (ms) of participants in Experiment 1 (left) and Experiment 2 (right) during stimulation or sham for both testing blocks of the Functional Semantic and Manipulation tasks. Standard error bars included. The asterisk marks the post-hoc analysis trend $p=.07$ further to the significant interactions.

3.5. Discussion

By using the neuromodulation technique tDCS, Study 2 directly assessed the neural correlates of object manipulation perception during the same perceptual task used in Study 1. Any modulatory effects of tDCS over the left IPL during perceptual functional semantic and manipulation decisions regarding the use of familiar objects would confirm whether this region is necessary in the perception of motoric action representations (manipulation), non-motoric action representations (functional semantic), or both. Based on the results from Study 1 confirming a selective disturbance in object manipulation perception in apraxia, an isolated effect of tDCS on manipulation decisions would support the assertion that the left IPL is the critical juncture where perceptual and action process are integrated via the ventro-dorsal sub-stream of the visual pathways model. Further, the use of parietal cathodal-inhibitory and anodal-excitatory tDCS across Experiment 1 and 2 would confirm whether anodal-excitatory stimulation is more likely to modulate performance during cognitive tasks (Jacobson et al., 2012) and whether tDCS is a viable rehabilitation technique for object-use errors in apraxia.

Examining the results from Study 2, the three-way interaction indicates that perception of object-use manipulation does seem to be modulated by left parietal cathodal-inhibitory stimulation (Experiment 1). Specifically, response times of perceptual decisions on the manipulation task were slower during the first test block compared to sham. No modulatory effects were seen during anodal-excitatory parietal stimulation (Experiment 2). Critically, neither cathodal-inhibitory nor anodal-excitatory parietal stimulation impacted reaction times when making functional semantic decisions. Response accuracy was unaffected by stimulation in either task.

The effect of left parietal cathodal-inhibitory stimulation on manipulation decisions is consistent with a wealth of neuroimaging data demonstrating increased left IPL activity during the perception of object-related action (Kellenbach et al., 2003; Boronat et al., 2005; Buxbaum et al., 2006; Canessa et al., 2008), and observation or pantomime of object-use (Chao & Martin, 2000; Mozaz et al., 2002; Rumiati et al., 2004; Frey, 2007; Vingerhoets, 2008; Króliczak & Frey, 2009; Vingerhoets et al., 2009; Caspers et al., 2010). Unlike the correlational link between left IPL and manipulation perception provided by neuroimaging, the effects of tDCS support a causal relationship between left IPL integrity and object manipulation perception.

These modulatory effects are consistent with Study 1 confirming a selective impairment in object manipulation judgements in apraxia, with approximately half of the apraxic patients having lesions implicating the left IPL. A direct relationship between left IPL integrity and manipulation perception has also been observed in other research; patients suffering from apraxia often show

deficits in object-related movements that are attributed to left IPL damage (Goldenberg & Hagmann, 1998; Johnson-Frey, 2004; Buxbaum et al., 2005; Buxbaum et al., 2007; Ishibashi et al., 2011; Sunderland et al., 2011; Myung et al., 2010; Lee et al., 2014). In combination, these findings indicate that the left IPL has an integral role in motoric action representations necessary for appropriate object-use. Therefore, although deficient gesture comprehension for transitive movement has been associated with disturbed inferior frontal regions for example, and appropriate object-use pantomime observed in patients with and without parietal lesions (Goldenberg et al., 2007; Pazzaglia et al., 2008; Bohlhalter et al., 2011), the results from Study 1 and 2 maintains that the left IPL plays an essential role.

Conversely, performance during the functional semantic task was unaffected when comparing sham to either left parietal cathodal-inhibitory or anodal-excitatory stimulation over the left IPL. In accordance with Study 1 with apraxic patients, these results not only suggest that non-motoric functional semantic action representations do not rely on the integrity of the left parietal cortex, but also that it is distinct from manipulation perception. As described in the previous study, research exploring dissociations in function and manipulation perception have overlooked the distinction between non-motoric action of how an object typically interacts with another object, and motoric action regarding how the actor handles the object for use. It remained possible that the left IPL was critical for the perception of object-related action whether it was motoric or non-motoric in nature. Subsequently, the selective effect of tDCS on manipulation perception with maintained functional semantic perception regarding object-use confirms that the left IPL is not required to perceive non-motoric action representations. Instead, consistent with representations of object function and functional semantic perception may be more closely associated with semantic processing in the ventral stream, relying on temporal regions (Sirigu et al., 1991; Bozeat et al., 2000; Boronat et al., 2005; Buxbaum et al., 2006; Negri et al., 2007; Canessa et al., 2008; Ishibashi et al., 2011; Chen et al., 2015).

Taken together, the distinct effect of tDCS on manipulation perception with maintained functional semantic perception regarding object-use adds weight to the proposal that motoric action representations are generated in the ventro-dorsal sub-stream. Through integration of known (ventral) and visible (dorsal) properties of objects, the ventro-dorsal stream enables objects to be grasped for use during motor execution, and the retrieval of postural requirements related to object-use using motor imagery (Rizzolatti & Matelli, 2003; Johnson-Frey et al., 2005; Buxbaum et al., 2006; Creem-Regehr, 2009; Binkofski & Buxbaum, 2013; Vingerhoets, 2014). This supposedly left lateralised stream is believed to extend from occipital cortex to the left IPL, to the ventral premotor cortex and frontal eye fields (Frey 2007; Rizzolatti et al., 2011). The current study suggests that disruption of the ventro-dorsal stream using left parietal tDCS impacts

prospective judgements about how objects should be grasped for use. However to support this argument more confidently, further investigation is required to achieve robust tDCS effects on motor imagery processes including manipulation perception.

Notably, tDCS had a somewhat marginal impact on manipulation decisions, where its effects were only seen during earlier trials (Block 1), but not during the later half of the task (Block 2). The discontinuous nature of the effect is somewhat difficult to interpret. Nevertheless, it was important to split the tasks in two blocks because, with so few parietal tDCS perception studies and none using continuous stimulation, it was uncertain whether the stimulation effect would be stable. As tDCS modulates cortical excitability rather than directly disrupting the neurons by causing an action potential (as with TMS), the effects of stimulation may change (Silvanto, Muggleton, & Walsh, 2008; Walsh, 2013) or be compensated for over time. Likewise, different cognitive processes may start to be recruited to compensate for the disruption of motor imagery, for example by relying on visual opposed to motor strategies. The current findings would support the idea that less efficient alternative strategies kick in with time as the accuracy scores in the second block were found to be consistently reduced in all tasks and in both stimulation protocols (in fact this is the only effect found on accuracy in this study). This would account for a mild, and over time weakening, effect of tDCS on cognitive function.

A study by Weiss and colleagues (2013) emphasises how modulation effects can change with minor alterations in electrode location. Anodal-excitatory tDCS applied to the left IPL improved motor planning when imitating meaningless hand gestures. However tDCS was only effective when the position of the target electrode implicated both adjacent regions of the left IPL: the supramarginal and angular gyri (area PFm). Performance was not modulated when either gyri was stimulated in isolation. This was achieved using neuronavigation to target cytoarchitectonically defined areas of the IPL. Given individual variance in head size and location of specific cortical regions, the marginal tDCS effects in the current study may therefore also be accounted for by the target electrode not targeting both supramarginal and angular gyri across all participants.

Nevertheless, the lack of tDCS effects in later trials calls into question its clinical efficacy for the neurorehabilitation of apraxic symptoms. In recent years direct-current stimulation has received considerable attention as a potential therapeutic technique for different clinical conditions. In this instance, any tDCS effects achieved during the perception of object-use in healthy populations would support its potential to improve object-use errors observed in apraxia. Although tDCS did modulate performance, the diminishing effects over time casts doubt over its generalised suitability as a rehabilitation technique. Instead, the current data emphasises the need to

investigate whether after-effects can be achieved when using parietal stimulation to improve performance during tasks heavily reliant on cognitive processes such as motor imagery training in neurorehabilitation (Ietswaart et al., 2011).

Furthermore, tDCS inhibiting the parietal cortex reduced performance but no effects of excitatory stimulation enhanced performance, despite recent reviews suggesting that achieving excitatory effects of stimulation during cognitive tasks are more likely (Nitsche & Paulus, 2011; Jacobson et al., 2012). A failure to improve task performance is also not encouraging when extending the application of tDCS from research to clinical use. Direct-current stimulation has however been shown to improve action planning for execution when anodal-excitatory stimulation is applied to the left parietal cortex. In addition to the study described above (Weiss et al., 2013), a study by Convento and colleagues (Convento, Bolognini, Fusaro, Lollo, & Vallar, 2014) confirmed that anodal left posterior parietal stimulation (with a cathode reference over the contralateral supraorbital ridge) improved speed of action planning when participants' were cued to perform certain actions. Methodologically, tDCS was applied at an intensity of two milliamps, which may have increased the effect of anodal tDCS. Referring again to Weiss and colleagues (2013) the direction of current flow through the left IPL and reference site area Cz (based on the 10-20 system for electrode placement) may also enhance the modulatory effects of tDCS. Despite successful modulation of movement planning, these studies imply that successful enhancement of performance using anodal-excitatory parietal tDCS over the left IPL may rely on planning for execution as opposed to a purely perceptual task.

Overall despite the lack of enhancing effects of tDCS in the current study, taken together these findings suggest that tDCS can modulate performance during the perceptual stages of action, including object manipulation decisions and movement planning for execution. Such data encourages the exploration of different electrode montages and stimulation intensities in an effort to achieve long-lasting and excitatory modulation effects of tDCS on performance.

In conclusion, the current results confirm a direct causal relationship between the left parietal lobe, in particular the left IPL, and the perception of object manipulation but not functional semantic knowledge regarding the use of familiar objects. Combined, the selective behavioural impairments of apraxic patients in Study 1 and the effects of tDCS on healthy populations in Study 2 suggest that the ventro-dorsal stream can be compromised directly through disruption of the left IPL, or indirectly by disturbing communication to regions along the pathway through white matter damage for example, whilst inferior parietal regions remain intact. Therefore it is likely that the left IPL has an integral role in motoric action representations necessary for

appropriate object-use and that disturbance to this region impairs the motoric elements of object-use.

Chapter 4

Study 3: Impaired integration of object visual affordances and stored knowledge in grasping: Evidence from apraxia.

4.1. Overview

By assessing the integrity of object manipulation and functional semantic representations for familiar objects, a selective deficit during the former condition in Study 1 and 2 indicate that internal movement representations attributed to the ventro-dorsal stream may be disrupted in apraxia. If stored representations from the ventral stream are less readily available to incorporate into action plans due to ventro-dorsal disruption, apraxia may also impair the ability to learn skilful manipulation of novel objects resulting in an over-reliance on objects' visual affordances during object-directed motor behaviour. Study 3 examined grasping performance of left hemisphere stroke patients with and without apraxia and age-matched healthy control participants when grasping cylindrical objects of differing weight distribution. Unlike control participants, a majority of apraxic patients failed to adapt their grasp when the object was unevenly weighted suggesting that stored representations of object-weight associations were not effectively incorporated into the action plan. Consistently central grasp-points along even and unevenly weighted cylindrical object suggests that these patients relied on the intact dorsal pathway to inform grasp behaviour. This abnormal grasping behaviour when known and visible information must be integrated corroborates the proposal that internal movement representations generated in the ventro-dorsal stream are disturbed in these patients. Disruption to this stream predicts that apraxic patients will not only have difficulty using familiar objects, but also when learning to skilfully manipulate novel objects on the basis of information other than low-level visual cues such as shape and size.

4.2. Introduction

In addition to impaired gesture imitation, apraxia is recognised by performance errors when demonstrating how objects are used (Goldenberg, 1995; Buxbaum, 2001). Although these errors are most apparent when pantomiming the use of objects with marked improvement during actual object-use, both pantomime and actual use can be affected (De Renzi & Lucchelli, 1988; Buxbaum & Saffran, 2002; Sunderland & Shinner, 2007; Goldenberg, 2009). Skilful manipulation of objects requires the integration of stored information about its typical use and

action processes enabling the object to be grasped appropriately based on its visual affordances and spatial location. As described in the general introduction, it is proposed that this integrative process is disturbed in apraxia. However it is not clear whether these deficits affect apraxic patients' ability to learn to manipulate novel objects.

Close examination of object knowledge in apraxic patients confirms that performance errors cannot be attributed to impaired ventral or dorsal streams of the visual pathways model; apraxic patients can identify visually presented objects (Daprati & Sirigu, 2006), use structural properties to appropriately reach and grasp familiar objects, and infer the use of novel objects based on their affordances (Sirigu et al., 1995; Goldenberg & Hagmann, 1998; Frey, 2007).

Recent evidence however suggests that a ventro-dorsal sub-stream of the traditional dorsal pathway is necessary when processing sensorimotor information based on long-term action representations of how objects are functionally used. This sub-stream may be implicated in apraxia. Through mutual connection with the ventral stream via the left IPL, perceptual information is incorporated into action plans (Rizzolatti & Matelli, 2003; Buxbaum & Kalénine, 2010; Rizzolatti et al., 2011; Binkofski & Buxbaum, 2013; Vingerhoets, 2014) enabling objects to be grasped for use by applying stored representations of how objects are functionally manipulated to the physical properties of the objects presented (Frey, 2007; Almeida, Fintzi, & Mahon, 2013; Garcea & Mahon, 2014).

If this sub-stream is disturbed in apraxia, the subsequent failure to effectively access and implement information from the ventral stream into the action plan, would result in an over-reliance on the intact dorsal stream. Consequently, objects are manipulated based on what is visually afforded irrespective of the goal of the action (Randerath et al., 2011). This theory however has been argued to place too much importance on different components of object knowledge; as argued by Goldenberg and colleagues (Goldenberg & Hagmann, 1998; Goldenberg, 2013) retrieval of knowledge of an objects prototypical use depends on previous experience, which cannot account for apraxic errors during novel object-use. However, this assumes that skilled object-use relies on the retrieval of information from “storehouses” rather than the convergence of short- and long-term visual representations depending on the goal of the motor act.

The proposal for impaired ventro-dorsal processing in apraxia not only stems from the established relationship between apraxic symptoms and damage to regions implicated in the ventro-dorsal stream, in particular inferior parietal regions (Haaland et al., 2000; Buxbaum, 2001; Buxbaum et al., 2006; Buxbaum et al., 2007; Frey, 2007; Goldenberg, 2009; Garcea & Mahon, 2014), but also

in performance errors during tasks assessing familiar object-use. As observed in Study 1, apraxic patients displayed a selective deficit in object manipulation perception (Chapter 2) whilst functional semantic perception was preserved, corresponding to previous research associating apraxia with impaired perception of the motoric elements of object-use (Buxbaum & Saffran, 2002; Rumiati et al., 2004; Vingerhoets et al., 2008; Myung et al., 2010). Focusing on action execution tasks, apraxics with left IPL damage responded abnormally when recognising and producing hand postures attributed to the use of familiar objects, but performed appropriately when grasping objects on the basis of their physical properties (Buxbaum et al., 2003). Assessing grip force, apraxic patients display poor anticipatory force control for familiar objects, but can successfully order familiar objects in weight order prior to grasping, confirming knowledge of object weight is intact (Dawson et al., 2010; Li et al., 2011). Over repeated lifts of these objects, apraxic patients do show appropriate fingertip force indicating that recent sensorimotor feedback can be used to guide force production over time (Gordon, Westling, Cole, & Johansson, 1993; Hermsdörfer, Li, Randerath, Goldenberg, & Eidenmüller, 2011; Randerath et al., 2011; Eidenmüller, Randerath, Goldenberg, Li, & Hermsdörfer, 2014). These results confirm that different mechanisms of the visual pathways model are important depending on the goal of the motor act and that the dorsal pathway is intact in these patients.

However, when making memory-driven reach and grasp movements, suggested to also rely on the integration of stored ventral representations and dorsal action processes, apraxic patients have shown equivalent performance to controls (Ietswaart et al., 2001; Dawson, et al., 2011). Although these findings suggest that apraxic patients can successfully utilise stored representations, it remains possible that the visuo-motor transformation involved in simple reach and grasp movements may not be difficult enough to place sufficient demand on high-level perceptual processes.

Despite the research outlined suggesting that apraxic patients have difficulties accessing and incorporating stored representations of actions related to skilled use of familiar objects, it remains unclear how these patients learn to manipulate new objects. Of the few studies have assessed this issue, Barde and colleagues trained patients to match novel gestures to novel object pictures that were high or low afforded by their associated objects. Apraxic patients demonstrated greater recognition of gestures highly afforded to the object shape (Barde, Buxbaum, & Moll, 2007). This affordance benefit was however only found for action recognition and not production where apraxic patients were consistently poorer than controls regardless of affordance. Use of two-dimensional objects during trainings might have reduced the affordance bias during action production. Retrieval of the appropriate action associated with the object may also have been more difficult when the goal was simply to produce the correct action (Barde et al., 2007).

The current study explored the impact of affordance on object manipulation by requiring participants to repeatedly lift and balance novel objects of differing weight distribution. Over three conditions the weight distribution of different cylindrical objects was indicated using different object-weight associations, either by low-level visual affordances of the objects structure, high-level visual affordance of a coloured ‘dot’ cue over the weighted end, or by an indirect high-level memory association with the colour of the object itself. Change in object manipulation over repeated lifts determined whether apraxic patients successfully used object knowledge obtained through experience to inform their grasp, or whether they continually relied on the visual cues to guide action.

Specifically, this study examined participants’ point of grasp along the object depending on weight distribution. When balancing objects healthy adults intuitively choose a grasp close to the centre of mass in order to minimise the energy required by grip force to compensate for load torque (Salimi, Frazier, Reilmann, & Gordon, 2003; Duemmler, Schoeberl, & Schwarzer, 2008; Endo, Wing, & Bracewell, 2011). This is said to be estimated visually prior to initial object grasping, which is reflected in accurate grasping of unfamiliar objects for the first time (Ledermen & Wing, 2003) or when asked to visually point to the centre of mass (Baud-Bovy & Soechting, 2001; Duemmler et al., 2008). The current task used action execution throughout as opposed to a perceptual task during learning. It was anticipated that apraxic patients would show greater performance accuracy when the object afforded the correct gesture with increased contextual information provided (akin to findings by Barde et al., 2007 in the recognition task).

During the low-level visually afforded condition, when weight distribution is indicated by object structure (i.e. the cylindrical object is evenly weighted), apraxic patients were expected to make initial grasps towards the centre of mass and require minimal trials to balance the object similarly to control groups. In the high-level visually afforded condition, when the centre of mass is indicated by a ‘dot’ over the weighted end, apraxic patients may benefit from this cue over time to prompt a more accurate grasp-point over each trial. Alternatively in the memory-associated condition, when the weight distribution is indicated indirectly by the colour of the object, apraxic patients were expected to be more profoundly impaired, requiring a greater number of trials to accurately balance the object. Instead, apraxic patients may continue to use low-level affordance cues of object structure to indicate weight distribution, resulting in more central grasps rather than to the left or right of the object. Inappropriate manipulation of high-level afforded and memory-associated objects with maintained use of low-level affordance cues, would confirm that apraxics over-rely on visual information processed by the dorsal visual stream due to ventral, stored

knowledge, being unsuccessfully incorporated into the action plan via the ventro-dorsal sub-stream.

4.3. Method

4.3.1. Participants

27 formally right-handed participants were recruited, 13 of which had suffered a stroke ($M_{\text{age}} 68 \pm 14$, 8 male) within 27 months ($M_{\text{months}} 15 \pm 10$) and 14 age-matched healthy control participants ($M_{\text{age}} 70 \pm 9$, 5 male). Of the patient group, at the time of testing three displayed symptoms of apraxia and 10 did not show signs of apraxia. Three of the non-apraxic stroke patients in this study had been classed as apraxic in the previous patient study (Chapter 2), however during the current apraxia screening, apraxic symptoms had largely resolved in the case of patient DF (96% correct) and WM (98% correct), whereas patient TM's apraxia had completely resolved (100%). Although patient TM's apraxic symptoms resolved quite rapidly, he initially only presented with very mild symptoms of apraxia (95% correct). One non-apraxic patient was later excluded (FR) as he was diagnosed with early onset of vascular dementia. Apraxia patient's AH, GW, and JA, presented with stable symptoms of apraxia across both studies. All participants gave informed consent to participate. The ethics committee within Northumbria University's Department of Psychology and a local NHS ethics committee approved the project.

On the basis of CT, MRI scans and clinical notes, patients who had suffered a brain haemorrhage or an infarct involving the left hemisphere were recruited from rehabilitation centres and National Health Hospitals within the North East of England. Patients presented with degrees of aphasia, right-sided weakness, or sensory loss. The presence of apraxia was classified on the basis of abnormal performance in one or more of the apraxia screening tools assessing gesture imitation and familiar object-use (pantomime and actual use). Patient details are described in Table 4.1 and apraxia screening performance in Table 4.3.

Table 4.2 describes each patient's lesion and the Brodmann areas implicated. Lesions were mapped using MRIcron software package (Rorden, Karnath, & Bonilha, 2007; <http://www.mccauslandcenter.sc.edu/mricro/mricron/>) based on the radiologist's MRI and/or CT clinical scans of each patient. The areas of damage for each patient were mapped using MRIcron software package; lesions were determined based on the radiologist's scan reports and the digital brain image. Scans were then normalised to a common stereotaxic space using Clinical Tool box software through SPM and applied to the Brodmann Atlas included in MRIcron (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012; <http://www.mricro.com/clinical-toolbox/>). Lesions for the three apraxic patients are visually documented in Figure 4.1.

Further test batteries and clinical notes were used to exclude any patient presenting with global cognitive deficits or known dementia, severe receptive aphasia or failure to follow one-stage commands (according to the language comprehension token test by De Renzi & Faglioni, 1978), or significant visuospatial neglect (according to the Apples Test by Bickerton et al., 2011).

Healthy age-matched control participants did not have a history of brain damage or stroke. These participants were recruited from the Psychology Department's participant database and were given monetary compensation for their time.

Table 4.1. Description of each apraxic patient in Study 3.

Featuring apraxics (top) and non-apraxics (bottom); includes FR who was excluded due to early onset vascular dementia.

Patient	Sex	Age at test (years)	Days post stroke at test	Right sided motor weakness on admission	Aphasia noted on admission	Neglect/hemianopia	Language comprehension (stage reached of Token Test)
AH	F	72	226	Y	Y	R neglect	6
GW	M	49	87	Y	Y	n.t.	3
JA	F	48	486	Y	Y	N	2
SG	F	66	833	Y	Y	N	6
TY	M	76	783	N	Y	N	5
DF	M	70	754	Y	Y	N	6
WM	M	78	152	Y	N	N	6
MB	F	49	142	Y	Y	N	6
TM	M	61	169	Y	Y	N	6
DJ	M	84	130	N	Y	N	5
JS	F	91	823	Y	N	N	6
BH	M	58	843	Y	N	N	6

Note. F: Female; M: Male; Y: Yes; N: No; L: Left; R: Right; n.t: Not Tested

Table 4.2. Description of each patient's lesion in Study 3.

Description of each apraxic (top) and non-apraxic (bottom) patient's lesion as described in the radiologist's CT and/or MRI reports and when mapped onto the Brodmann atlas.

Patient	Includes IPL	Lesion – left hemisphere lesion information on basis of acute CT/MRI report	Brodmann Areas damaged (% = amount lesioned)		
			>75%	25-75%	<25%
AH	N	L MCA infarct involving L putamen, internal capsule, & caudate head. Extending into L frontal white matter.	34		10, 11, 25, 32, 47, 45, 46
GW	Y	L temporo-parietal, basal ganglia, & parieto-occipital infarcts.		22, 31, 37, 39	6, 19, 20, 34, 36, 38
JA	N	L MCA infarct	34, 38	47	6, 11, 20, 21, 22, 41, 44
SG	N	L corona radiata infarct.			
TY	N	L frontal MCA infarct.		47	11, 38
DF	-	L fronto-temporo-parietal infarct & L insula.			
WM	-	L total anterior circulation infarct.			
MB	N	L frontal lobe, thalamus, lentiform, R caudate head, bilateral basal ganglia lacunar infarcts.			
TM	N	Ischaemic change in the L MCA occlusion.			42
DJ	N	L frontal MCA infarct	44	6, 38, 43	9
JS	N	Mild white matter ischaemic change.			
BH	N	L thalamus bleed.			

Note. F: Female; M: Male; Y: Yes; N: No; L: Left; R: Right; ACA: Anterior Cerebral Artery; MCA: Middle Cerebral Artery.

Brodmann areas ascribed to the inferior parietal lobe (areas 39 & 40) are indicated in bold. Only the scan report details are included for WM because his scan could not be obtained for digitation, and for DF because the scan was performed too early to allow accurate localisation of the lesion.

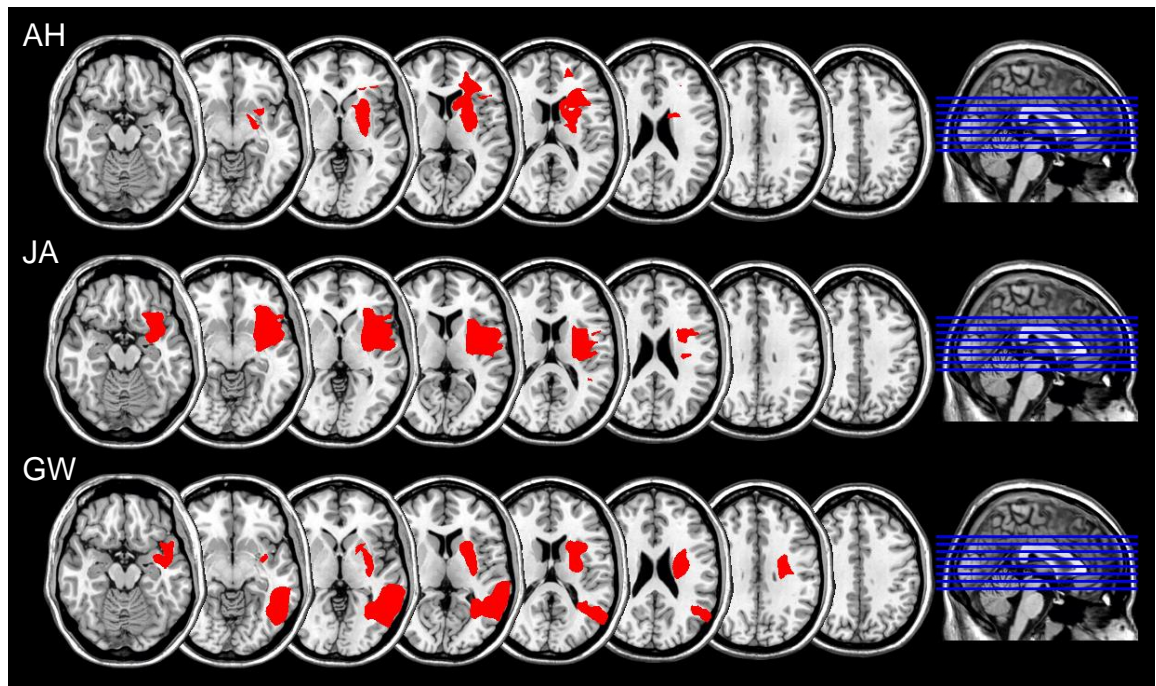


Figure 4.1. Scan slices of lesions of each patient in Study 3.

Scan slices for apraxic patients AH, JA, and GW; lesioned areas were applied to a template scan allowing clear visualisation of the anatomical landmarks. The lesion area(s) are in red. Left is right as per neurological convention.

4.3.2. Materials

Apraxia Screening

Gesture imitation of hand and finger postures (Goldenberg, 1996). The experimenter demonstrated different hand postures relative to the head and finger postures irrespective of the hands position in relation to the body. Gestures were performed ‘like a mirror’; the experimenter sat opposite the patient, performing each posture with their right hand to be imitated by the patients’ left hand after the demonstration had ended. Successful imitation of each gesture on the first trial was awarded two points; one point was given if the patient was successful after a further demonstration; zero points if the gesture was not imitated correctly. A total score of 20 could be achieved by imitating ten gestures of each kind.

Pantomime of object use (based on Goldenberg et al., 2007). Participants were required to demonstrate the use of 19 objects. The experimenter presented a drawn image of each object (taken from Cycowicz et al., 1997) and named the action to be pantomimed. Points were given for the presence of predefined movement features (Goldenberg et al., 2007 details these). With exception to demonstrating the use of scissors, body-part-as-object errors were marked as incorrect. A total of 53 points could be obtained, with less than 43 measured as pathological.

Actual object use (based on De Renzi & Lucchelli, 1988). Participants were given the same verbal description of the action to be demonstrated as in the pantomime task. Eighteen of the pantomimed objects were presented; one point was given if used correctly and zero if incorrect. The incorrect use of two or more objects was considered pathological.

Table 4.3. Apraxia screening performance of patients in Study 3.

Screening performance and error types in apraxics (top) and non-apraxics (bottom).

Patient	Apraxia Screening							
	Gesture Imitation (total score)				Object use (total score)			
	Hand (20)	Errors	Fingers (20)	Errors	Pantomime (53)	Errors	Actual (18)	Errors
AH	19	<i>fe</i>	19	<i>fe</i>	37	<i>bpo; ss; gm</i>	18	
GW	16	<i>hm; sm</i>	4	<i>p of hands; sm</i>	10	<i>ao; aa</i>	16	<i>aa</i>
JA	19	<i>sm</i>	20		36	<i>bpo; ss; gm; sm</i>	16	<i>ss; sm</i>
SG	20		20		53		18	
TY	18	<i>sm</i>	18	<i>sm</i>	48	<i>bpo; sm</i>	18	
DF	18	<i>hm</i>	20		50	<i>gm; sm</i>	18	
WM	20		20		48	<i>gm; sm</i>	18	
MB	19	<i>hm</i>	19	<i>sm</i>	53		18	
TM	20		20		53		18	
DJ	18	<i>hm</i>	19	<i>fe</i>	53		18	
JS	20		20		53		18	
BH	20		20		51	<i>ss</i>	18	

Note. Types of performance error were given the following acronyms: GESTURE IMITATION: perseveration (p); hand misorientation (hm): misorientation of the hand relative to the face; finger extension (fe): incorrect fingers extended from hand; spatial misorientation (sm): hand misorientation relative to the experimenter, e.g. back of hand instead of palm facing. OBJECT USE: action addition (aa): miscellaneous actions not interpretable as a step in the task, e.g. waving; action omission (ao): failed to perform any recognisable action; step omission (so): failed to complete some parts of the movement, e.g. rotating hand when squeezing a lemon; body-part-as-object (bpo): e.g. brush teeth with finger; semantic substitution (ss): e.g. stir with fork; grasp misestimation (gm): incorrect grasp size/type for object, e.g. pincer grip for cup; spatial misestimation (sm): incorrect relationship between object relative to body or another (reference) object.

Object Grasping Task

Object stimuli. Five cardboard cylinder tubes (length: 24.5cm, diameter: 3.7cm) were used, each containing a 17-gram weight (length: 2cm, diameter: 1.5cm) in one or both ends. The five cylindrical objects comprised of three conditions: ‘low-level visually afforded’, ‘high-level visually afforded’, and ‘memory-associated’. The low-level visually-afforded condition consisted of one ‘neutral’ grey object that was evenly weighted with one weight in each end of the cylinder. The high-level visually afforded condition consisted of two grey objects that were unevenly weighted, containing a weight in either the left or right end of the object. The heavier end of each object was marked with a red ‘dot’ (1cm diameter), which acted as a visual cue of the weight distribution when acting upon the object. Finally, the ‘memory-associated’ condition consisted of one green and one blue cylinder; when presented to the participant, the green object was weighted on the left, whereas the blue object was weighted on the right. Participants were required to remember the colour-weight associations when lifting the object without a visual cue indicating weight distribution on either end of the cylinder. In addition to the main objects, two white practice cylinders were used when giving task instructions: one evenly-weighted (length: 42cm, diameter: 1.5cm) and one unevenly-weighted object (length: 46, diameter 1.7cm, 34-gram weight on the right side). The practice cylinders did not resemble test objects in size and weight to minimise priming effects of grasping these objects prior to the main experiment.

A horizontal bar (length: 30cm, diameter: 0.5cm) was positioned perpendicular to the participant, 35cm in front of the participant and 24cm above the table. Both the experimenter and participant used the bar to indicate the extent to which the object was balanced. For the duration of testing a video camera was placed behind the horizontal bar and recorded each trial. A schematic representation of the experimental setup can be seen in Figure 4.2.

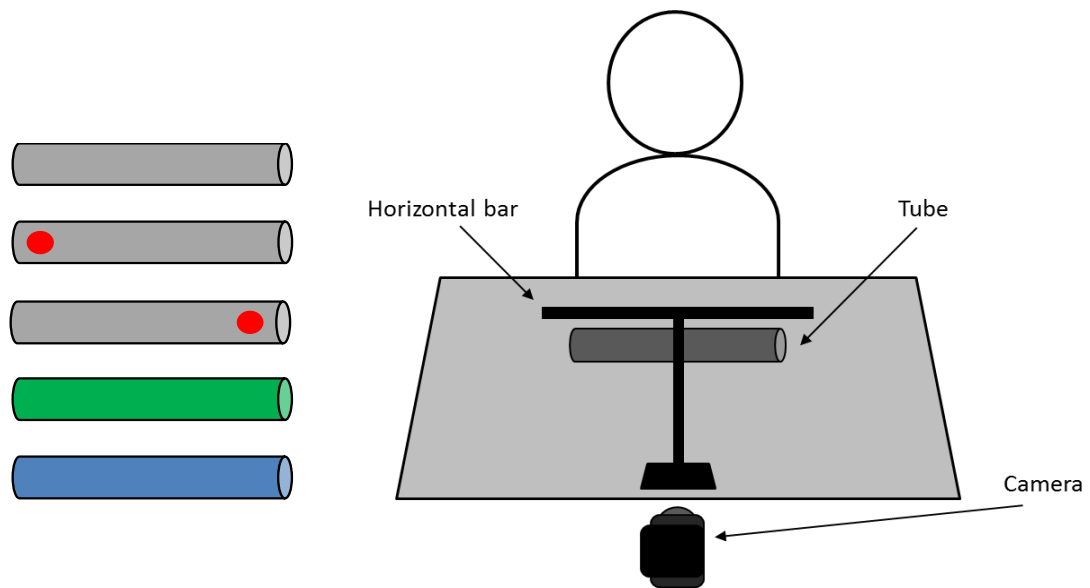


Figure 4.2. Schematic representation of the experimental setup of Study 3.

(Left) Objects used in the main task. From top: low-level visually afforded; left & right weighted high-level visually afforded with ‘dot’ cue; left weighted/green & right weighted/blue memory-associated. (Right) Schematic representation of the experimental setup.

4.3.3. Procedure

Each participant was seated at the workspace where the objects were presented. Using the horizontal bar as a guide, participants were instructed to lift and balance each object using a pincer grip with the index and thumb of their left hand. After the object was lifted to the horizontal bar, participants returned the object to the table and removed their hand from it before another trial began. It was emphasised that if the object was imbalanced, they should not compensate by tightly pinching the object or rotating their wrist during or at the end of each lift. Task instructions were demonstrated using the evenly weighted practice cylinder. Participants were then requested to practice the task procedure using the same cylinder. Once participants successfully completed the movement they were presented the unevenly weighted practice cylinder and repeated the process. After it was evident that participants understood the procedure, the main task was started. During the main task, to ensure each participant had the same experience with the object, they were asked to lift and balance each object five times before being presented the next object. In each block, objects were presented in a random order. Overall, there were five testing blocks in which participants saw each object once; including each individual trial, participants lifted each object 25 times, totalling 125 trials. The video camera recorded participants completing each trial.

4.3.4. Data Analysis

Task performance across each condition was initially compared between each control group (healthy and non-apraxics) using a two-way mixed model ANOVA exploring OBJECT (low-level visually afforded; high-level visually afforded; memory-associated) x GROUP (Healthy vs. Non-apraxic controls) to rule out differences across control groups. Each apraxic patient was then compared to the control groups separately using modified t-tests recommended when estimating the abnormality of an individual patient's score against a control sample that is modest in size (Crawford & Garthwaite, 2002; Crawford, Garthwaite, & Porter, 2010). Participants were assessed on change in performance accuracy over trials (TC) and change in performance accuracy over blocks (BC). The former would indicate whether apraxic patients' performance improved with repeated lifts of the same object and the latter would confirm whether apraxic patients applied what they had learned in previous blocks when each object was reintroduced. The point at which the object was grasped was used as a guide to evaluate grasp behaviour.

Firstly, in order to analyse the video footage, photo snapshots were created when participants were at the maximal point of object lift. From each snapshot, the 'point of grasp' was measured based on the midpoint position of the index finger along the object (from right to left).

Grasps were considered accurate depending on whether the object was successfully balanced and an appropriate point of grasp was applied to compensate for the objects weight distribution. This ensured participants were accurate due to adjusting their grasp-point along the object, as opposed to applying greater grip force or by rotating their wrist during each lift. If the location of an individual's grasp was greater than two standard deviations from the 'optimum' point of grasp (OP) to compensate for weight distribution, it was marked as inaccurate. The optimum point of grasp was measured for each object based on healthy control participants mean point of grasp for the fifth trial across all blocks.

Accuracy change over Trials (TC). Grasp accuracy was compared between Trial 1 and Trial 5 across blocks. Performance change across trials would indicate whether apraxic patients' performance improved with repeated grasps of the same object. To compare performance, accuracy was first weighted; accurate grasps in early trials (e.g. Trial 1) received a greater weighting compared to accurate grasps in later trials (e.g. Trial 5). This reflected the extent to which performance was driven by trial and error or learning each objects weight distribution. Inaccurate grasps were given a negative score: fewer points were deducted when grasps were inaccurate in early trials and greater points deducted when performing inaccurately in later trials. These reflected the extent to which participants failed to adapt their grasp based on each objects' weight distribution with repeated grasps of the same object (see Table 4.4 for weighted scores). As a greater score could be achieved in Trial 1 compared to Trial 5, these scores were then

calculated as proportions of the maximum score achievable in that trial, across all five blocks. For example, in Trial 1 an accurate grasp scores 5 points, over 5 blocks a maximum score of 25 can be achieved, whereas for Trial 5 an accurate grasp scores 1 point, over 5 blocks a maximum score of 5 can be achieved. Once participants' scores in Trial 1 and Trial 5 were transformed into proportions, accuracy in Trial 5 was deducted from Trial 1 (as outlined in the equation below). Based on this calculation, a greater negative score signifies improved accuracy across trials, a positive score signifies reduced or consistently poor performance across trials, and a score of zero indicates that the participant achieved the highest accuracy across trials.

$$\text{Accuracy change (TC)} = (\text{block 1-5 average score}^{\text{trial 1}} / \text{maximum score}^{\text{trial 1}}) - (\text{block 1-5 average score}^{\text{trial 5}} / \text{maximum score}^{\text{trial 5}})$$

Accuracy change over Blocks (BC). Using the same calculation, performance across blocks was assessed by comparing the average accuracy across trials between Block 1 and Block 5. Performance change across blocks would confirm whether apraxic patients applied what they had learned in previous blocks when each object was reintroduced. As with trial data, performance across blocks was weighted using positive and negative scores. In early blocks, participants received greater points for accurate grasps and fewer points were deducted for inaccurate grasps, whereas in later blocks participants received fewer points for accurate grasps and more points were deducted for inaccurate grasps. Scores were transformed into proportions of the maximum score before accuracy in Block 5 was deducted from accuracy in Block 1.

Notably during testing, non-apraxic patients BH and JS completed only four testing blocks due to experiencing fatigue when lifting the objects several times. The same calculation applied to the final block was instead applied to Block 4 for these patients.

Table 4.4. Accuracy score weighting for Study 3.

Weighted scores for analyses of accuracy change over Trial and Block.

Trial	1	2	3	4	5
Correct	5	4	3	2	1
Incorrect	-1	-2	-3	-4	-5
Block	1	2	3	4	5
Correct	5	4	3	2	1
Incorrect	-1	-2	-3	-4	-5

4.4. Results

In order to confirm whether apraxic patients utilised low-level visual cues, high-level visual cues, and memory-associations regarding weight distribution when balancing each object, performance change across trials and across blocks were assessed. Point of grasp for each object was used as a guide to evaluate grasp behaviour. These results would indicate whether apraxia impacts the ability to learn to skilfully manipulate new objects in a manner applicable to impaired internal movement representations attributed to the ventro-dorsal stream.

4.4.1. Accuracy change across trials (TC)

Healthy controls versus non-apraxics. An initial two-way mixed model ANOVA exploring Object (low-level visually afforded; high-level visually afforded; memory-associated) x Group ruled out differences in performance change across Trials in healthy and non-apraxic controls. Non-significant main effects confirmed that performance was comparable across control groups (Group: $F_{(1,21)} = .139$, $p = .713$, $\eta_p^2 = .007$) and between objects (Object: $F_{(1.357,28.504)} = 3.583$, $p = .058$, $\eta_p^2 = .145$). However, a significant interaction Object x Group ($F_{(1.357,28.504)} = 8.479$, $p = .004$, $\eta_p^2 = .288$) was identified. Independent samples t-test did not reveal significant differences in performance for all conditions ($p > .05$) except the low-level visually afforded condition ($t_{(21)} = 2.353$, $p = .028$). Non-apraxics showed greater improvement in task performance from Trial 1 to 5 (TC = $-.333 \pm .280$) on the Neutral, evenly weighted object compared to healthy controls whose performance reduced (TC = $.257 \pm .714$). Notably, differences easily arise on the evenly-weighted, low-level visually afforded object, because the point scoring system works with difference from the mean and standard deviation on this condition in normal performance is very small (and differences are therefore of limited interest).

Despite variances in performance change for the Neutral object, healthy and non-apraxic controls consistently grasped the object close to the optimum grasp-point (OP = 13.18cm). Examining grasp-point behaviour of controls across all three conditions, both groups initially grasped closer to the centre of each object in Trial 1, but by Trial 5 were ≤ 1.32 cm from the optimum grasp-point for each object. This indicates that healthy and non-apraxic controls effectively utilise both low- and high-level visually afforded and memory-associated information to improve performance when repeatedly lifting each object (see Table 4.5 for performance change over trials, Table 4.6 for participants average points of grasp, and Figure 4.3 for accuracy change across trials).

Patient AH. Single case t-tests confirmed that during the high-level visually afforded condition, patient AH performed significantly worse than both healthy controls ($p < .001$, $t = 13.363$) and non-apraxics ($p = .007$, $t = 3.160$) with at least a minimum of 99.33% of controls falling below AH's score. When grasping memory-associated objects, patient AH was also significantly worse than healthy ($p < .001$, $t = 17.100$) and non-apraxic controls ($p = .001$, $t = 4.775$) with at least a

minimum of 99.93% of controls falling below AH's score. For both high-level visually afforded and memory-associated conditions, AH's accuracy was consistently poor ($TC \geq 2.52$) whereas control groups generally improved performance across trials (TC from 0.045 to -0.274).

Observing the average grasp-points for both the high-level visually afforded and memory-associated conditions, patient AH maintained a point of grasp towards the centre of each object (from 11.10cm to 13.45cm). These grasps were at least 4.8cm from the optimum grasp-point to compensate for weight distribution of each object. Unlike control groups, patient AH did not adjust her grasp towards the weighted end of across trials.

As this patient did not adjust her grasp away from the midpoint, when grasping the Neutral low-level visually afforded object AH's performance change was comparable to both healthy controls ($p=.367$, $t = -.0348$; an estimated 36.68% falling below AH's score) and non-apraxics ($p=.271$, $t = 1.128$; an estimated 85.40% falling below AH's score). Not only does this data confirm that patient AH successfully uses low-level information afforded by the structure of the object, but also AH's use of midpoint grasps confirms that her visual neglect did not affect grasp performance.

Patient GW. Performance of patient GW mirrored that of patient AH. Performance change over trials was worse than healthy and non-apraxic controls when grasping unevenly weighted objects in both the high-level visually afforded and memory-associated conditions: for all comparisons $p \leq .001$, with at least an estimated 99.93% of controls falling below GW's score. Patient GW was consistently unsuccessful in balancing these objects ($TC = 4.8$ for each), with average points of grasp ranging from 13.46cm to 14.76cm across all four objects, and at least 5.18cm from the optimum grasp-point. Overall, GW's average grasp was consistently close to or slightly to the left of each objects centre regardless of their weight distribution.

However when grasping the Neutral low-level visually afforded object, GW's performance was comparable to both healthy ($p=.367$; an estimated 36.68% falling below GW's score) and non-apraxic controls ($p=.146$; an estimated 85.40% falling below GW's score). Patient GW's average grasp-points were close to the optimum point of grasp. This also confirms that GW does not have any symptoms of neglect that might affect performance.

Patient JA. Apraxic patient JA's performance change across trials was comparable to both healthy and non-apraxic controls for low-level visually afforded and memory-associated conditions ($p > .05$; an estimated 25.65% to 61.96% of controls falling below JA's score). During the high-level visually afforded condition, although JA was comparable to non-apraxics ($p = .349$, $t = 0.402$; an

estimated 65.10% of controls falling below JA's score), performance change was significantly different to healthy controls ($p = .005$, $t = 3.032$; an estimated 99.52% of controls falling below JA's score). Unlike the other conditions, JA did not greatly improve grasp accuracy between Trial 1 to 5 (TC=.360) in the high-level visually afforded condition, indicating that JA continued to make errors by the final trial. However, as indicated by average grasp-points in Trial 1 and 5, JA typically reoriented her grasp towards the weighted end of each object, grasping ≤ 1.31 cm from the optimum grasp-point, discounting Trial 5 of right-weighted object. In fact, when grasping the right-weighted object, JA deviated to a more extreme rightward grasp in a seemingly compensatory purposeful way; average grasp-point was 4.20cm further right than the optimum point (6.29cm) by Trial 5, whereas grasp-points of healthy controls were less than half a centimetre from the optimum point. Grasping behaviour of JA further suggests that she was using compensatory mechanisms; JA performed the task slowly and deliberately by delaying grasp onset and slowly lifting each object, whereas AH and GW would rapidly reach and grasp each object during each trial. Together, average grasp-points confirm that JA generally reoriented her grasp towards the weighted end of each object, however she continued to make errors by Trial 5.

Table 4.5. Patients' grasp performance change in Study 3.

Performance change over trials (TC) and blocks (BC) in non-apraxic (top) and apraxic (bottom) patients.

PT	Change across trials (TC)			Change across blocks (BC)		
	Low-level Visually Afforded	High-level Visually Afforded	Memory-Associated	Low-level Visually Afforded	High-level Visually Afforded	Memory-Associated
SG	-0.24	-0.24	-0.48	0	0.48	-0.36
TY	0	0.6	1.2	0	0.24	0
DF	0	-0.12	-0.48	0	-0.12	-0.24
WM	-0.48	-0.165	-0.84	1.2	0.28	2.16
MB	-0.48	-0.84	-0.6	1.92	0.12	-0.24
TM	-0.48	-0.24	-0.96	0	-0.12	0.36
DJ	-0.72	0.36	-0.12	1.2	-0.36	0
JS	0	1.65	1.8	-1.5	1.65	1.8
BH	-0.6	-0.6	-0.9	1.5	-1.11	-1.99
Ave	-0.333	0.045	-0.153	0.48	0.118	0.166
AH	0	2.52	4.8	0	3.24	4.8
GW	0	4.8	4.8	0	4.2	4.8
JA	-0.24	0.36	-0.84	0	-0.72	0.48

4.4.2. Accuracy change across Blocks (BC)

Healthy controls versus non-apraxics. Non-significant main effects and interactions from the two-way mixed model ANOVA confirmed that performance change across Blocks was

comparable between control groups: Object, $F_{(1.288,27.045)} = .986$, $p = .381$, $\eta_p^2 = .045$, Group $F_{(1,21)} = .385$, $p = .542$, $\eta_p^2 = .018$, Object x Group $F_{(1.288,27.045)} = .264$, $p = .671$, $\eta_p^2 = .012$. Both healthy and non-apractic controls adjusted their point of grasp across blocks depending on the weight distribution of each object (see Table 4.5 for performance change over trials, Table 4.6 for average grasp-points and Figure 4.3 for accuracy change across blocks); grasps were $\leq 1.32\text{cm}$ from the optimum grasp-point by the final block. Accuracy was also maintained across blocks (BC ranged from .094 to .583).

Patient AH. Accuracy change was worse than both healthy and non-apractic controls during the high-level visually afforded and memory-associated conditions (for all comparisons $p < .05$, with at least an estimated 99.65% of controls falling below AH's score). Patient AH's score for accuracy change across blocks was consistently high ($\text{BC} \geq 3.24$) compared to both control groups ($\text{BC} \leq .583$). Average grasp-points confirm that AH did not adjust her grasp according to the weight distribution of each object but maintained a more central grasp; across both Block 1 and Block 5, AH's grasp-point ranged between 11.50cm and 13.45cm, at least 5.20cm from the optimum point of grasp. This suggested that AH failed to utilise stored knowledge of weight distribution when the object was reintroduced.

As before, patient AH's performance change was comparable to healthy ($p = .344$, $t = -0.411$; an estimate of 34.38% of controls falling below AH's score) and non-apractic controls ($p = .339$, $t = -0.430$; an estimate of 33.94% of controls falling below AH's score) when grasping the Neutral low-level visually afforded object. Patient AH's accuracy was consistently high ($\text{BC} = 0$) and maintained a central grasp-point within 1.48cm from the optimum point of grasp.

Patient GW. Similarly, during the high-level visually afforded and memory-associated conditions patient GW performed worse than healthy controls and non-apraxics; for all comparisons $p < .05$, with at least an estimated 96.76% of controls falling below GW's score. Patient GW grasped each object centrally at least 5.18cm from the optimum grasp-point resulting in a consistently poor accuracy change across blocks ($\text{BC} \geq 4.20$).

Mirroring patient AH, when grasping the Neutral low-level visually afforded object, GW's performance change was equivalent to healthy ($p = .344$, $t = -0.411$) and non-apractic controls ($p = .339$, $t = -0.430$). Patient GW maintained a central point of grasp within 1.77cm from the optimum grasp-point resulting in a consistently high accuracy change score ($\text{BC} = 0$).

Patient JA. Across all three conditions (low-level visually afforded/high-level visually afforded/memory-associated) patient JA's performance was comparable to controls ($p > .05$; an

estimated 12.60% to 67.27% of controls falling below JA's score). Average grasp-points consistently accounted for the weight distribution of each object in Block 1 and Block 5, confirming she was able to adjust her grasp when the objects were reintroduced.

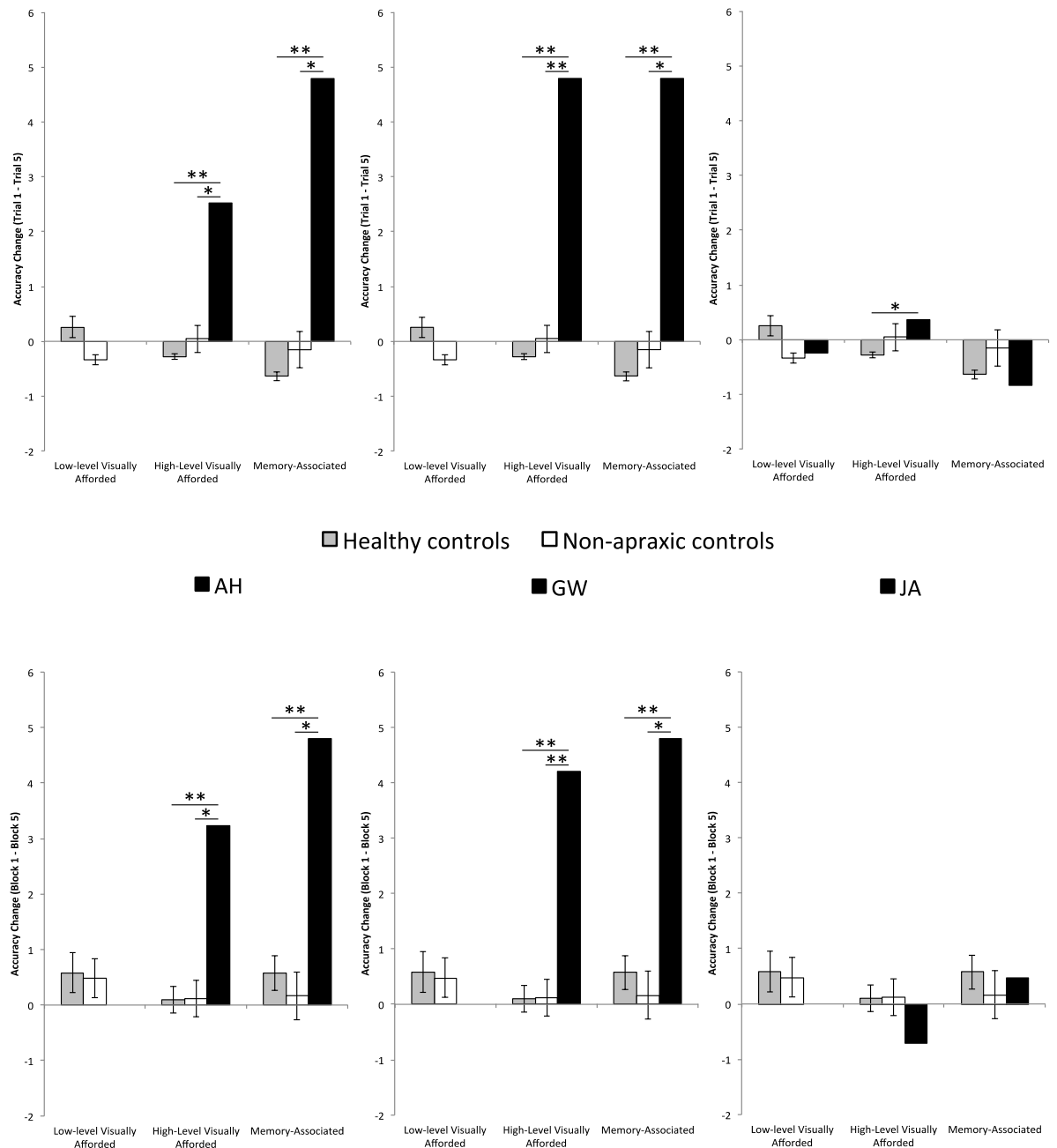


Figure 4.3. Patients change in grasp accuracy between Block 1 and 5 in Study 3.

(Top) Change in grasp accuracy between Trial 1 and Trial 5 across blocks including standard error bars. (Bottom) Change in grasp accuracy between Block 1 and Block 5 across trials including standard error bars. For both Trial and Block analyses a negative score indicates an improvement in performance across trials; a positive score indicates a reduced or consistently poor performance. Scores close to zero reflect consistent high accuracy across trials. Two asterisks denotes a p value $<.001$, and a single asterisk, a p value $<.05$.

Table 4.6. Average points of grasp across trials and blocks in Study 3.

Point of grasp (cm). Top: Trial 1 and 5 across blocks, including the overall average point of grasp and standard deviation across every trial for each object. Bottom: Block 1 and 5 across trials, including the overall average point of grasp and standard deviation across every block for each object.

Point of grasp (distance from OP)										
Trial	Low-Level Visually Afforded		High-Level Visually Afforded (Dot)				Memory-Associated			
	Evenly Weighted (OP=13.18)		Left Weighted (OP=19.85)		Right Weighted (OP=6.29)		Left Weighted (OP=20.18)		Right Weighted (OP=6.30)	
	1	5	1	5	1	5	1	5	1	5
AH	11.70 (1.48)	11.55 (1.63)	11.75 (8.10)	12.00 (7.85)	12.00 (-5.70)	11.10 (-4.80)	11.50 (8.69)	12.55 (7.63)	12.00 (-6.83)	11.35 (-6.18)
GW	13.30 (-0.12)	13.60 (-0.42)	13.65 (6.20)	13.95 (5.90)	12.95 (-6.65)	13.00 (-6.70)	13.70 (6.49)	15.00 (5.18)	13.60 (-8.43)	13.55 (-8.38)
JA	14.30 (-1.12)	12.85 (0.33)	20.70 (-0.85)	18.54 (1.31)	5.55 (0.75)	2.10 (4.20)	17.10 (3.09)	21.30 (-1.12)	15.70 (-10.53)	2.55 (2.62)
Healthy control	13.48 (-0.29)	13.18 (0.01)	17.48 (2.37)	19.84 (0.01)	9.60 (-3.31)	6.30 (0)	14.09 (6.10)	20.21 (-0.03)	11.53 (-6.36)	5.15 (0.02)
Non-apraxic	11.91 (1.33)	12.57 (0.58)	16.45 (3.45)	19.05 (0.89)	9.23 (-3.01)	5.88 (0.33)	13.48 (6.80)	19.04 (1.22)	11.26 (-6.07)	5.62 (-0.52)
Block	1	5	1	5	1	5	1	5	1	5
AH	11.70 (1.48)	11.70 (1.48)	11.80 (8.05)	12.55 (7.30)	11.75 (-5.45)	11.50 (-5.20)	12.10 (8.08)	13.45 (7.30)	11.70 (-6.53)	12.60 (-7.43)
GW	12.70 (0.48)	14.95 (-1.77)	14.10 (5.75)	15.40 (4.45)	13.50 (-7.20)	13.90 (-7.60)	15.65 (4.53)	15.40 (4.45)	13.95 (-8.78)	14.35 (-9.18)
JA	12.60 (0.58)	12.65 (0.53)	6.74 (13.11)	21.95 (-2.10)	5.70 (0.60)	2.20 (4.10)	20.85 (-0.67)	20.80 (-2.10)	6.55 (-1.38)	4.80 (0.37)
Healthy control	12.86 (0.32)	12.99 (0.19)	16.66 (3.19)	19.89 (-0.04)	7.80 (-1.51)	6.58 (-0.28)	17.98 (2.20)	19.32 (-0.04)	7.43 (-2.25)	6.28 (-1.11)
Non-apraxic	13.10 (0.08)	11.37 (1.32)	16.47 (3.39)	19.77 (0.50)	7.69 (-1.39)	5.37 (-0.01)	16.93 (3.25)	18.96 (0.50)	8.86 (-3.39)	5.21 (-0.58)

Note: OP = optimum grasp-point to compensate for objects' weight distribution.

4.5. Discussion

To assess whether apraxic patients successfully integrate stored knowledge of objects into action plans, participants were required to learn different weight distributions when lifting and balancing objects using a pincer grip. Over three conditions, each objects' weight distribution was indicated by either a low-level visually afforded cue (object structure), high-level visually afforded cue (visible dot over the weighted end), or memory-associated cue (object colour). If apraxic patients fail to incorporate stored information into their grasp, performance would decrease linearly with increased reliance on high-level information (i.e. when object structure did not afford weight distribution). As a result, apraxic patients were instead expected to over-rely on visual information, resulting in more centrally oriented grasps (based on object structure) disregarding the location of the objects' centre of mass. The results from this study would not only confirm whether apraxic errors are restricted to skilled object-use, corresponding to those observed in Study 1, but also whether apraxia affects patients' ability to learn skilful use of new objects.

Performance change across trials (TC) and across blocks (BC) in the low-level visually afforded condition confirmed that all apraxic patients (AH, GW, & JA) successfully grasped and balanced the neutral, evenly weighted object. Comparably to healthy and non-apraxic controls, during consecutive grasps of the neutral object (TC) and when grasping the object as it was reintroduced in later blocks (BC), apraxic patients' central grasp-points remained close to the optimum point of grasp to compensate for weight distribution. Accurate grasping performance during the low-level visually afforded condition indicates that apraxic patients can successfully manipulate objects when the weight distribution is indicated by the objects' structure (symmetrical cylinder). The traditional dorsal stream of the visual pathways model is therefore intact in these patients, allowing appropriate use of visual information to accurately reach and grasp objects on the basis of their shape and size (Goodale & Milner, 1992; Milner & Goodale, 2006). This is consistent with previous studies exploring manipulation behaviour in apraxia, confirming that these patients can effectively grasp objects for transfer and infer the use of novel objects based on their affordances (Sirigu et al., 1995; Goldenberg & Hagmann, 1998; Buxbaum et al., 2003; Ietswaart et al., 2006; Frey, 2007; Randerath et al., 2009; Randerath, Goldenberg, Spijkers, Li & Hermsdörfer, 2010; Sunderland et al., 2013).

Although patient JA's performance was within the normal range (see below for a discussion of JA's pattern of results) during the high-level visually afforded and memory-associated conditions, patients AH and GW failed to update their grasp-point when the objects were unevenly weighted in both conditions.

For both the high-level visually afforded and memory-associated conditions, patient AH and GW maintained a central grasp-point during recurrent trials with the same object (TC) or when the objects were reintroduced in later blocks (BC). Failure to compensate for load torque by reorienting grasps towards the centre of mass suggests that these apraxic patients fail to integrate acquired knowledge regarding objects into action plans. Inaccurate grasp-points persisting into the final test block is particularly representative of this. Paired with unimpaired behaviour in the low-level visually afforded condition, grasp performance of patients AH and GW suggests an over-reliance on the structural properties afforded by the object. Maintained central grasp-points in the high-level visually afforded and memory-associated conditions indicate that AH and GW continually referred to intact dorsal processing allowing accurate on-line reach-to-grasp behaviour and use of low-level visual cues of weight distribution.

Patient AH and GW's performance is compatible with previous research indicating impaired perception of skilled object-use (Buxbaum & Saffran, 2002; Buxbaum et al., 2003; Myung et al., 2010) and is consistent with the behaviour observed in Study 1 (Chapter 2) where apraxic patients demonstrate impaired perception of object manipulation. Together with appropriate semantic and functional semantic perception of objects, these results suggest that errors are restricted to the motoric elements of object-use whilst the ventral stream of the visual pathways model is preserved in these patients. The performance of patient AH and GW adds to research exploring action execution in apraxia; apraxic patients frequently choose inappropriate non-functional grasps (Randerath et al., 2009; Randerath et al., 2010; Sunderland et al., 2010) or demonstrate impaired grip force for familiar objects (Gordon et al., 1993; Dawson et al., 2010; Hermsdörfer et al., 2011; Eidenmüller et al., 2014). Consequently, the performance of patient AH and GW across all three conditions offers direct evidence in support of the proposal that the ventro-dorsal stream is compromised in these patients, resulting in impaired performance when grasping asymmetrically weighted objects. Confirmation that the impairment lies at the ventro-dorsal level comes from the fact that dorsal processing of object structure remains intact, as does ventral processing of semantic and functional semantic perception (Study 1). Therefore these results offer unique evidence that ventro-dorsal disruption appears to not only impair skilled use of familiar objects, but also the ability to learn to manipulate novel objects.

Interestingly, both patients AH and GW did not appear to benefit at all from the visual cue in the high-level visually afforded condition and there was no evidence of learning. In healthy populations when an object is asymmetrically weighted, grasp-points typically migrate towards the weighted end, particularly when visual cues indicate where the centre of mass is located (Endo et al., 2011). Apraxics use of familiar objects also improves from pantomime to actual-use with increased affordance or contextual cues (De Renzi & Lucchelli, 1988; Buxbaum & Saffran, 2002;

Sunderland & Shinner, 2007; Goldenberg, 2009; Randerath et al., 2011). Although apraxic patients would not use the high-level visually afforded cue as effectively as control participants, it was hypothesised that the presence of increased visual information in the form of a 'dot' over the weighted end might prompt more appropriate grasps in later trials or when the object was reintroduced.

It is possible that a symbolic visual cue, such as a dot, is not ecologically meaningful and subsequently requires more explicit learning. This differs from implicit visual geometric cues of shape and size that are ecologically meaningful (Gentile, 2000; Salimi et al, 2003). Consequently the explicit learning of a visual dot-weight association may also be reliant on higher order perceptual processes to conceptualise the meaning of the dot cue. If this is the case, comparable performance in the high-level visually afforded and memory associated conditions may be due to both requiring integration of stored and visible information via the ventro-dorsal stream. Therefore, it is reasonable that apraxic patients AH and GW might not benefit from the high-level visual cue. Studies showing improved apraxic performance with increased contextual information may be attributed to an increased presence of low-level affordance cues regarding the objects' size and structure, however as very few studies have assessed learning of skilled movement in apraxia this can only be speculated. The results of the current study therefore emphasise the need to explore learning in apraxia to determine what type of cues these patients can successfully utilise to inform their grasp.

Additionally, it was somewhat surprising that patients' AH and GW did not benefit from short-term sensorimotor feedback to improve grasp performance during subsequent trials within a block (TC). Attributed to the bilateral dorsal stream, rapidly decaying sensorimotor memory is formed and updated with repeated grasps of the same object (Bursztyn & Flanagan, 2008; Buxbaum & Kalénine, 2010). Apraxic patients apply appropriate fingertip force when repeatedly lifting novel objects, suggesting sensorimotor memories can be formed and applied (Gordon et al., 1993; Ietswaart et al., 2001; Dawson et al., 2010; Li et al., 2011; Hermsdörfer et al., 2011; Randerath et al., 2011; Eidenmüller et al., 2014). However, more central grasp-points remained fairly constant between the first and last trial in the current study. AH and GW may fail to update their-grasp points with repeated lifts due to visible structural information and short-term sensorimotor feedback being in conflict; object shape suggests a central weight distribution whereas sensorimotor feedback indicates it is either to the left or the right of the object. In grip force studies, the novel objects were typically symmetrical with a central weight distribution; the shape of the novel object corroborated sensorimotor feedback of object weight, resulting in improved fingertip force with repeated lifts (for examples see Gordon et al., 1993; Dawson et al., 2010; Li et al., 2011). Consequently it is argued that failure to use short-term sensorimotor feedback by

patient AH and GW is not because this process is disrupted, but that the design of the current task causes an impediment between visual and sensorimotor information leading to low-level visual affordance cues to be favoured. Taken together, the performance of patient AH and GW in high-level visually afforded and memory-associated conditions confirms that they fail to incorporate stored knowledge into action plans. Once more, these results emphasise the need to explore the capabilities of apraxic patients to learn skilful use of new objects.

Although not quite normal, apraxic patient JA performed comparably to control groups in all conditions, except when compared to healthy controls during repeated grasps (TC) of the high-level visually afforded objects. Exploring JA's behaviour when grasping high-level visually afforded objects, a positive score for accuracy change over trials indicates that JA continued to make errors by the final trial. These errors were only minor in contrast to patient AH and GW who consistently failed to adjust their grasp-point according to weight distribution. Further, unlike these patients, no individual healthy control or non-apraxic patient failed to adapt their grasp-point over repeated lifts (TC) and when the objects were reintroduced (BC).

Of note, non-apraxic participant JS did not perform as efficiently as the other non-apraxic patients in the high-level visually afforded and memory-associated conditions. However, she was still markedly more accurate than AH and GW. Patient JS also performed at ceiling during the language comprehension test and apraxia screening indicating that her performance was not applicable to poor comprehension or apraxia. Instead, her performance may be more attributable to her age; JS is the oldest participant (91) and testing had to be terminated after the fourth test block as she became fatigued.

Referring back to apraxic patient JA, when comparing JA's grasp behaviour to patient AH and GW, it is possible that she is using compensatory mechanisms to improve performance. Both AH and GW performed the task very quickly, immediately reaching for the object at the start of each trial and rapidly lifting the object before returning it to the table. Alternatively, JA, a young and highly motivated patient, performed the task slowly and deliberately, delaying grasp execution and gradually lifting each object. After the task, JA commented that when the object was placed in the testing area, she observed whether one end of the object landed on the table first as a potential clue to its weight distribution. Despite careful placement of each object to avoid this issue, it may be beneficial to occlude participants' view when objects are placed on the table. However, it was felt that participants should have a strong sense of object permanence; the presence of each object during testing ensured that participants were aware that each object reintroduced in later trials was the same as those seen previously. Although patient JA may have been using compensatory techniques to complete the task, it is apparent that she is able to adjust

her grasp with repeated trials and then apply knowledge gained from earlier blocks to accurately grasp objects when they were reintroduced. Patient JA's improved performance compared to AH and GW cannot be attributed to better comprehension, as JA scored the least in the language comprehension test. Likewise, JA did not suffer from milder apraxic symptoms; patient GW demonstrated the more severe apraxic symptoms whereas JA's apraxic behaviours were comparable to AH. Finally, JA's lesion is very similar to that of AH.

For patient JA either ventro-dorsal processing remained intact or through her careful performance she managed to assemble compensatory strategies even at this high-level afforded stage. However this cannot be verified. Appropriate performance when behaviour is delayed in apraxic patients suggests that stored knowledge is maintained but difficult to access. As described, accurate memory-driven reach and grasp performance is observed when apraxic patients pick up basic blocks based on simple size and distance information (Ietswaart et al., 2001). During semantic judgements apraxic patients also showed greater fixations on object pictures that were manipulation-related to the target word (e.g. "typewriter" and "piano") when the manipulation relationship was not task relevant; the fixation position was comparable to the non-apraxic control group but the effect emerged later (Myung et al., 2010). The magnitude of delayed activation of manipulation related action information in apraxia is predicted by poorer object-use pantomime performance and the extent to which inferior parietal and posterior temporal regions were compromised (Lee, Mirman, & Buxbaum, 2014). Therefore, the extended delay between reach and grasp movements used by JA in her slow and deliberate performance (compared to patient AH and GW who initiated grasps immediately) may have enabled her to incorporate stored knowledge into action plans. This may also indicate why JA continued to make grasping errors by the final trial when grasping the high-level visually afforded objects.

Although the design of the current study delayed reach-to-grasp action between trials by requiring participants to return their hand to the table before beginning another grasp movement, the duration of this delay was not controlled. Further investigation is required to confirm whether delay between reaching and grasping can reduce performance errors when balancing novel objects. It is probable that such compensatory strategies may rely on critical brain structures being intact; JA presented with frontal lesions that implicate white matter whilst parietal regions remain undamaged (as was the case in AH). In contrast, GW's lesion implicates temporal and parietal regions of the left hemisphere suggesting that the critical juncture between the ventral and dorsal pathways may be compromised (Rizzolatti & Matelli, 2003; Buxbaum & Kalénine, 2010; Rizzolatti et al., 2011; Binkofski & Buxbaum, 2013; Vingerhoets, 2014). This corresponds with patient GW's markedly poor performance across all apraxic tests. Based on research showing a strong association between impaired object-use and temporal and parietal damage (Goldenberg,

2009; Vingerhoets, 2014), and the results of Study 2 confirming an relationship between left IPL integrity and motor imagery performance, disturbed use of high-level visually afforded and memory-associated information is expected in this patient.

In conclusion, the current study confirms that apraxic patients have intact dorsal processing allowing successful grasping of objects' whose weight distribution is indicated by low-level visual affordance information of object structure. Apraxia was furthermore associated in some patients with a disrupted ability to utilise high-level visually afforded or memory-associated information indicating weight distribution. Specifically, patient AH and GW failed to successfully incorporate high-level visually afforded information in the form of a visual dot cue over the objects weighted end, and memory-associated information where weight distribution was indicated by the objects colour. Grasps were inaccurate during repeated lifts and when the objects were reintroduced. A third apraxic patient (JA) seemed to compensate for these difficulties. Crucially, the abnormal grasping behaviour in apraxic patients AH and GW suggests that integration of visible and known object properties attributed to the ventro-dorsal stream is impaired. Not only does disruption to ventro-dorsal processing impair use of familiar objects, but also these results would predict that apraxia is associated with difficulty learning to manipulate new objects. If apraxic patients only benefit from low-level visual affordance cues such as shape and size, these patients may fail to adapt their behaviour over time if these cues do not correspond to the appropriate functional grasp.

Chapter 5

Study 4: The efficacy of using parietal tDCS to evaluate the laterality of motor and visual imagery using hand and object mental rotation tasks.

5.1. Overview

Throughout this thesis it has been emphasised that the left hemisphere is purported to have a dominant role in motor imagery, in particular the left parietal cortex. This contrasts visual imagery that recruits predominantly right parietal regions. Based on the accumulated findings of Study 1 and 3 indicating a relationship between the ventro-dorsal stream and apraxia, and Study 2 confirming the critical role of the left IPL during manipulation perception, Study 4 further assessed the necessity of the left IPL during motor imagery. As tDCS is a novel technique in imagery research and given its weak effect in Study 2 and variable nature during cognitive tasks, the efficacy of modulating motor imagery was assessed using classic mental rotation tasks. These hand and object mental rotation tasks have been reliably shown to evoke motor and visual imagery respectively. Using different electrode montages, Experiment 1 and Experiment 2 examined changes in performance accuracy and reaction times when participants rotated hands or objects. Results confirmed that depending on where the electrodes are placed, tDCS has differing effects on performance. Nevertheless, although weak, motor mental rotation performance was modulated by stimulation of left parietal regions suggesting this region is critical during motor imagery, which is left lateralised. The laterality of visual imagery however was less clear despite being intended as a classic and reliable control condition.

5.2. Introduction

5.2.1. Motor and Visual Imagery

Mental imagery refers to the ability to create and manipulate mental images in the absence of the stimulus (Kosslyn, 1994). This conceptual process is built up of different forms including motor and visual imagery. As described in the general introduction (Chapter 1) motor imagery can be generalised as the mental simulation of a motor act when the imager mentally performs movement of their own body-part without actually moving them, and without subliminally tensing the engaged muscles (Crammond, 1997; Jeannerod, 1994; Lotze & Cohen, 2006). It is affected by the actual body posture, biomechanical constraints, and by the inertial properties of the body parts

(Parsons, Gabrieli, Phelps, & Gazzaniga, 1998). When individuals imagine a movement and are asked to estimate the time taken to conduct it, such as tapping each finger with the thumb or walking to a target in the room, the estimates given are very similar to the time taken to actually perform the tasks (Milner, 1986; Decety & Jeannerod, 1996; Jeannerod, 1997). Imagined movements also conform to Fitts's Law of the direct relationship between movement difficulty and time taken to perform; the more difficult a movement is to perform, the longer it takes to complete it, both in imagery and actual movement (Decety, 1991; Decety & Jeannerod, 1996).

Similarly, visual imagery is based on the formation of visual mental images from visual resources in the absence of imagining one's own body-parts (Annett, 1995; Sirigu & Duhamel, 2001). It has been shown to be influenced by visuospatial parameters, such as the relative size of imagined objects (Stevens, 2005; Pelgrims, Andres, & Olivier, 2009) and the distance an object needs to be rotated when comparing to another; participants need longer to make judgements about objects or characters that are rotated at increasing amounts from the upright position (Cooper and Shepard, 1973; Kosslyn, DiGirolamo, Thompson, & Alpert, 1998).

Mental rotation tasks are frequently used when determining the cortical loci of motor and visual imagery processes; it is suggested that individuals perform the task by mentally rotating an internal representation of an object in space, which can rely on motor or visual imagery depending on task demands. Two classic mental rotation tasks have been shown to implicitly involve these different forms of imagery. Motor imagery is commonly assessed with mental rotation of body-parts, such as the hand. A hand mental rotation task created by Parsons (1987) requires participants to confirm whether the left or right hand is displayed when presented individually on a screen at different orientations. Response times have been shown to conform to physical constraints outlined above, including Fitts's law and the biomechanical constraints of the hand posture (Decety & Jeannerod, 1996). For example, participants are considerably slower at declaring handedness if the palm of a hand is presented upside down compared to upright as it is a more unnatural posture. Visual imagery is evoked when rotating external objects. Shepard and Metzler (1971) demonstrated that the time required determining whether two visual objects are identical or incongruent increases linearly with the angular discrepancy between the orientations of the two stimuli (Overney & Blanke, 2009). This effect has also been shown with two- and three-dimensional objects and alphanumerical figures (Pelgrims, et al., 2009).

5.2.2. Laterality of motor and visual imagery

Motor and visual simulations have been proposed to activate the corresponding mechanisms to action movement and vision. When referring to motor imagery, it has been consistently shown to activate the fronto-parietal motor network involving neural mechanisms underlying actual

movement execution (Fogassi & Luppino, 2005; Rizzolatti & Craighero, 2004). Visual imagery on the other hand appears to activate the parieto-occipital visual perception network (Kosslyn et al., 1998; Zacks, Vettel, & Michelon, 2003a; de Lange, Hagoort, & Toni, 2005). A common region of activation in both these imagery tasks is the posterior parietal cortex (PPC).

Of particular interest to this study, is the suggestion that motor imagery evokes greater activation of the left than the right parietal cortex; in addition to the involvement of the left IPL during object manipulation perception as confirmed in Study 2 of this thesis, a left hemisphere bias for motor imagery appears predominantly in mental rotation tasks (Haaland et al., 2004; Johnson-Frey et al., 2005; Muhlau et al., 2005). From such research it has been argued that the ability to mentally rotate body parts may be functionally separate from the ability to rotate external objects. This proposal supports the findings obtained in Study 2 of this thesis, where cathodal-inhibitory stimulation of the left IPL reduced performance during object manipulation perception (Chapter 3).

Neuroimaging research supporting this pattern has shown that when participants are required to mentally rotate body parts, increased activity is mostly found in the left hemisphere and parietal lobe (Bonda, Petrides, Frey, & Evans, 1995). This was also confirmed in an event-related potential mapping study on mental transformation of body parts (Overney, Michel, Harris, & Pegna, 2005; Overney & Blanke, 2009). When directly comparing mental rotation of external objects and body parts, Kosslyn and colleagues (1998) found bilateral activation in the parietal lobes for three-dimensional cubes and purely left hemispheric activation for hands, including the precentral gyrus, premotor area, inferior and superior parietal lobe, insula, and superior frontal cortex. This is consistent with the established dominance of the left hemisphere in motor control (Sabate, Thimm, Hesse, Kust, Harbe, & Frink 2004).

Conversely, the classical view of visual imagery is that visuospatial information is processed predominantly in the right posterior parietal cortex (Corballis, 1997; Dong et al., 2000; Tomasino et al., 2003b; Zacks, Gilliam, and Ojemann 2003a; Zacks et al., 2003b). Exclusive right hemisphere involvement has been found when rotating alphanumeric characters and objects, including activation of the right superior parietal cortex (Pegna et al., 1997; Harris et al., 2000; Harris & Miniussi, 2003; Jordan, Heinze, Lutze, Kanowski, & Jancke, 2001; Vingerhoets et al., 2001; Zacks et al., 2003b).

However, some research has shown contradictory evidence, with left hemispheric bias for alphanumeric characters (Alivisatos and Petrides, 1997; Vingerhoets et al., 2001), or bilateral activity in both intraparietal regions for similar stimuli (Carpenter, Georgopoulos, & Pellizzer,

1999; Cohen et al., 1996). Such research suggests that both two hemispheres may contribute to the mental rotation of visual stimuli (Mellet, Petit, Mazoyer, Denis, & Tzourio, 1998; Jordan et al., 2001; Feredoes and Sachdev, 2006). A recent study by Pelgrims and colleagues (2009) investigated these inconsistencies by stimulating the supramarginalis gyrus and superior parietal lobule (considered important for motor and visual imagery respectively) using repetitive transcranial magnetic stimulation (rTMS). When completing the hand laterality task, rTMS equally affected performance when applied to either hemisphere irrespective of the hand displayed (left or right). Furthermore, they found identical deficits in visual imagery regardless of whether the right or left hemisphere was being stimulated. Therefore, it was suggested that there is not a hemispheric bias for visual or motor imagery.

The body of evidence exploring dissociable activations in visual and motor imagery through mental rotation have yielded inconsistent results. However, although activation has been found unilaterally or bilaterally in these tasks, neuroimaging cannot confirm which brain regions are critical during these processes and which may play a supportive role in mental rotation. Specifically, it may be that motor imagery recruits both the spatial and motor processes in order to successfully mentally rotate body-parts, or that right hemisphere spatial processing during motor imagery is supplementary. Evidence from neuropsychology or neuromodulation studies give a direct indication of how performance changes when either the left or right hemisphere has been compromised.

Neuropsychological evidence further supports the argument for hemispheric laterality of motor and visual imagery, with patients presenting double dissociations in their ability to accurately rotate objects or body parts (Sirigu et al., 1996; Sirigu & Duhamel, 2001). For example, Tomasino and colleagues (2003a) found that patient MT, with fronto-temporo-parietal damage, showed a selective deficit in mentally rotating hands when determining hand laterality. MT however was able to mentally rotate three-dimensional external objects. Overney and Blanke (2009) found similar behaviour in a patient with left posterior parietal brain damage implicating the IPL, whose deficit predominated for pictures of right arms and an inability to distinguish between anatomically possible and impossible arm positions. This behaviour contrasts that of patient JB who showed impaired mental rotation of three-dimensional external objects but maintained motor imagery ability (Sirigu & Duhamel, 2001).

Posterior right hemisphere brain-damaged patients have also shown impairment in mental rotation of external objects, however some of which were not tested on rotation of body parts (Bricolo, Shallice, Priftis, & Meneghello, 2000; Ditunno & Mann, 1990). When directly comparing the ability of unilateral right or left hemisphere brain-damaged patients to mentally rotate hands or

objects, Tomasino et al. (2003b) also found a double dissociation. They found a consistent deficit in hand laterality discrimination in left hemisphere damaged patients, and maintained mental rotation of external objects. Conversely, right hemisphere patients showed the opposite effect (Rumiati, Tomasino, Vorano, Umiltà, & De Luca, 2001). From such research it was inferred that a functional double dissociation exists between rotation of body parts (i.e. motor imagery) and of external objects (visual imagery) that seem to reflect complementary specialisations of the opposite hemispheres.

5.2.3. Current studies

Using transcranial direct current stimulation (tDCS) as a neuromodulatory technique to condition the parietal cortex, the aim of the following studies was to shed light on the proposed left lateralisation of motor imagery. Using a classic contrast between visual (object) and motor (hand) mental rotation tasks, Experiment 1 explored the modulatory effects of parietal direct-current stimulation on participants' reaction times and response accuracy; the balance of the two parietal cortices were modulated by inhibiting the one while exciting the other and vice versa. Based on the theory of hemispheric rivalry first described by Kinsbourne (1977), the parietal lobes compete to orient attention to the contralateral hemisphere. Similarly to modulating the interparietal balance of attention, bilateral parietal electrode placement may disturb the balance between the left and right hemispheres. Based on inconsistencies in the purported effects of tDCS and the weak stimulation effects found in Chapter 3 during object manipulation perception, Experiment 2 explored the efficacy of direct-current stimulation in mental rotation tasks using three different electrode montages: a repeat of the cathodal-inhibitory and anodal-excitatory stimulation of the left and right parietal cortices but with adapted control visual imagery stimuli, unilateral parietal cathodal-inhibitory with contralateral neutrally placed frontal anodal reference, and unilateral parietal anodal-excitatory with contralateral neutrally placed frontal cathodal reference. This aimed to shed light on both the nature of the laterality effects found in Experiment 1 and to further establish the appropriate tDCS protocol when examining cognitive laterality tasks involving the parietal cortex.

As outlined in the methodology section of the general introduction of this thesis, tDCS alters neurons resting membrane potential; anodal-excitatory stimulation causes neurons to depolarise and cathodal-inhibitory stimulation causes them to hyperpolarise. Behaviourally these changes are reflected in an increase of performance in the former and decrease in performance for the latter (Nitsche et al., 2008; Nitsche & Paulus, 2011). However, evidence suggests that stimulation effects can vary depending on the electrode montage used.

A key issue coming to light is that the effect of tDCS on behaviour can vary considerably depending on where the electrodes are placed on the head. Although anodal-excitatory and cathodal-inhibitory effects have been found fairly robustly in experiments looking at motor functions (for example Stagg et al., 2009), these effects have not been consistently replicated in cognitive studies. Jacobson and colleagues (2012) explored the discrepancies between tDCS effects on motor and cognitive tasks found that achieving stimulation effects in cognitive tasks was highly variable. In particular, the review suggested that excitatory effects were achieved considerably more during cognitive tasks compared to inhibitory effects. As application of tDCS during cognitive tasks involving parietal regions are in their infancy, it is important to explore this issue.

Another concern when applying tDCS is the distance between electrodes. When tDCS is applied, two electrodes are placed on the scalp and the direct-current run from cathode to anode. Classic electrode placement involves one electrode being placed over the cortical area of interest whilst the other acts as a reference over a distant, neutral site (see Feurra et al., 2011 for example). Alternatively, in recent studies both electrodes have been placed bilaterally over areas of interest (for example see Sparing et al., 2009). However, by placing the electrodes bilaterally, there is increased risk of the direct current “shunting” (Wagner et al., 2007; Nitsche et al., 2008). In other words, if the electrodes are close together, the current may run shallowly through the scalp rather than penetrating the cortical areas of interest. This can result in a reduction or absence of stimulation effects on task performance. Further, unilateral or bilateral electrode placement alters the direction of current flow, which have also been shown to alter the effect of stimulation (for reviews see Nitsche et al., 2008; Nitsche & Paulus, 2011).

Together, Experiment 1 and 2 explored the motor imagery laterality debate using different tDCS protocols. Given that motor imagery has shown left lateralised or bilateral activity, tDCS was applied during mental rotation of hands to confirm whether one or both hemispheres are critical. As a control condition, the effect of tDCS on visual imagery was examined using an object mental rotation task. Based on the classic assumptions regarding the polarity effects of tDCS, it was hypothesised that due to the established evidence, right parietal cathodal-inhibitory stimulation would reduce task performance during object mental rotation. If however mental rotation of hands differs from objects different tDCS effects were anticipated; if motor imagery is left hemisphere dominant, cathodal-inhibitory stimulation over the left parietal cortex would reduce task performance during the hand mental rotation task.

5.3. Experiment 1: Laterality of motor and visual imagery using cathodal-inhibitory and anodal-excitatory stimulation of the left and right parietal cortices.

5.3.1. Method

Experiment 1 of this study explored the proposal that internal movement representations are left lateralised. Using classic mental rotation tasks shown to be reliant on motor imagery (Bonda et al., 1995; Kosslyn et al., 1998; Overney et al., 2005) and disturbed after left hemisphere damage (Sirigu et al., 1996; Sirigu & Duhamel, 2001; Tomasino et al., 2003a; Tomasino et al., 2003b; Overney & Blanke, 2009), stimulation was applied to both the left and right parietal cortices by inhibiting one while exciting the other and vice versa. In correspondence with the mild effects of left IPL cathodal-inhibitory stimulation reducing performance during object manipulation judgements (also reliant on motor imagery) observed in Study 2 of this thesis (Chapter 3), it was anticipated that left parietal cathodal-inhibitory and right parietal anodal-excitatory stimulation would also reduce performance in the hand mental rotation task, but potentially with greater effect due to the modulation of the interhemispheric balance.

Design. A within-subject repeated-measures design was used with three independent variables: Task (hand/object mental rotation), Stimulation Protocol (left parietal cathodal-inhibitory & right parietal anodal-excitatory, left parietal anodal-excitatory & right parietal cathodal-inhibitory/sham), and Rotation Difficulty Rank (1/2/3/4). Participants' reaction time for correct responses (RT) and response accuracy (%) were measured.

Participants. An opportunity sample of 20 participants was recruited ($M_{\text{age}} 22.2 \pm 5.8$, 13 female). All participants were right handed (laterality quotient 88.33) in accordance with the revised Edinburgh Handedness Inventory (Oldfield, 1971; Cohen, 2008). Participants gave informed consent and received a health-screening questionnaire based on Rossi, Hallett, and Rossini (2011) to confirm their eligibility for tDCS stimulation. As compensation for their time, participants were given money or were offered course points as part of students' undergraduate programme. Three participants were excluded from the final analyses; two achieved an average accuracy <70%, and one did not follow the experimental procedure correctly.

Apparatus and Materials. Transcranial direct current stimulation (tDCS) was applied during both tasks using a battery driven stimulator (Magstim, UK). Stimulation was applied to the scalp through 25cm² electrodes inserted into saline soaked sponges, totalling 0.06mA intensity, which is within the safety limits for healthy volunteers (Nitsche et al., 2003). To minimise cutaneous sensation, the stimulation current was increased gradually to the desired intensity by ramping up

the current for 10 seconds; total stimulation duration per participant was approximately 20 minutes ($M_{\text{minutes}} 18.3 \pm 4.3$).

Electrodes were placed over both the left and right parietal cortices and oriented to run parallel to the central sulci in accordance with the international 10/20 system for electrode placement. Based on previous literature, the centre of each electrode was placed approximately over the inferior parietal lobes (IPL); the centre of each electrode was positioned between P3 and CP3, and P4 and CP4 (based on electrode placement from Harris and Minuissi, 2003). Over three sessions participants received either cathodal-inhibitory stimulation over the left parietal cortex and anodal-excitatory over the right parietal cortex (LPc/RPa), cathodal-inhibitory stimulation over the right parietal cortex and anode-excitatory over the left parietal cortex (LPa/RPc), or sham stimulation. During sham the electrodes were placed on the head and stimulation was turned on for 30 seconds so that the participant could feel the initial stimulation sensation. The stimulator was then switched off before the tasks began. Including the sham condition, participants took part in three separate testing sessions. To minimise possible carry over effects of tDCS, each session took place on separate days at least two days apart.

Stimuli. Stimuli were presented using E-Prime (Psychology Software Tools, Pittsburgh, PA) on a 19-inch computer monitor (1280 x 1024 pixels) at a viewing distance of 63cm. In the hand mental rotation task, a depiction of a single hand was presented in the centre of the screen and participants indicated through button presses whether a left or right hand was displayed. Stimuli consisted of drawn hands taken from Parsons (1994) presented from four viewing angles: back and palm of the hand, side from thumb, and side from fifth finger. Each viewing angle was presented equally with left and right hands.

During the object mental rotation task, participants were presented with four different three-dimensional (3D) objects created from 10 cubes, based on Vandenberg and Kuse (1978) drawings and modified by Peters et al (1995). On each trial, two 3D objects were presented simultaneously; on the left of the screen the object was presented in the upright position (target object), whereas the object on the right (rotated object) was presented in eight different orientations that rotated on the x or z axes. The object on the right was either the same as the object on the left or a vertical mirror image. Both hand and object stimuli were presented upright (0 degrees), and rotated clockwise by 45, 90, 135, 180, 225, 270, 315 degrees (see Figure 5.3.1 for examples of stimuli and stimulus presentation).

Procedure. Participants attended three sessions where both the hand and object mental rotation tasks were completed whilst one of the stimulation protocols was applied. At the beginning of

each session, participants were given a verbal instruction of the testing procedure before the tDCS stimulation was applied to the scalp and participants were given a few seconds to get used to the sensation. Stimulation remained online whilst participants completed both hand and object mental rotation tasks. During testing, participants rested their head in a chin rest and each task began with another written instruction emphasising quick but accurate responses. On screen, individual trials consisted of a central fixation cross for 500ms prior to the task stimuli. Once the task stimuli appeared on the screen participants had an unlimited time to respond. Responses were recorded using the keyboard number pad; using the left index finger, participants pressed '1' when a 'Left' hand or 'Same' object was presented, and using the right index finger, participants pressed '3' when the 'Right' hand or 'Mirrored' object was presented. It was requested that participants close their fists apart from the index fingers to ensure they could not use their hands as visual cues when completing the hand mental rotation task. It was also emphasised that participants should not move their head or hands to aid mental rotation.

The hand mental rotation task consisted of 160 trials; participants observed all stimulus conditions for the back and palm of the hand three times, and all stimulus conditions for the side from thumb and side from fifth finger twice. The object mental rotation task consisted of 128 trials where each stimulus condition was presented once. Each task had a short break in the middle. Once the tasks were completed, stimulation was switched off. Session two and three followed the same procedure with the alternate stimulation protocol. Stimulation protocol and presentation order of each mental rotation task was counterbalanced across participants. Pseudo-randomisation of trials ensured the same stimuli were not presented consecutively.

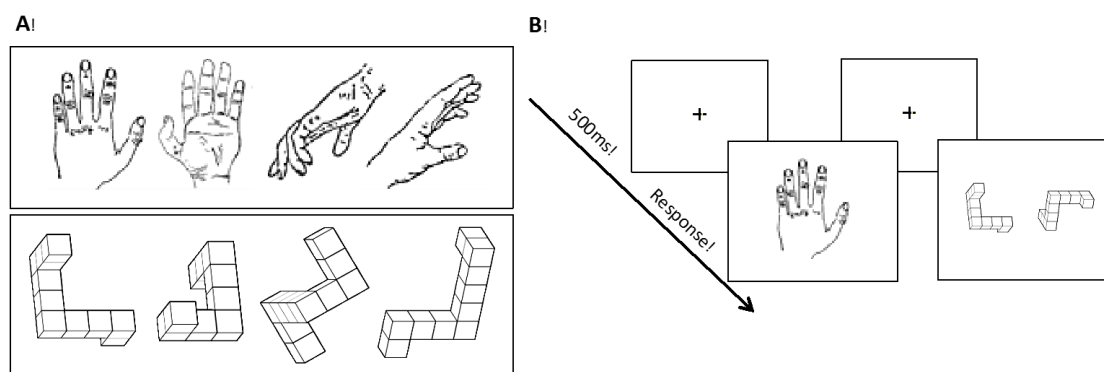


Figure 5.3.1. Hand and object stimuli for Experiment 1 of Study 4.

(A) Example of hand and 3D object stimuli used for each task. (B) Time course of stimulus presentation.

Data Analysis. Three-way repeated-measures analyses of variance (ANOVA) were run to explore the data. To account for the stimuli being presented in several viewing positions (for example, back and palm of the hand), both hand and object stimuli orientations were converted to a 'rank';

the orientation of each object was ranked linearly on the difficulty of mental rotation from one (easiest) to four (hardest). For example, with regard to biomechanical constraints, rotating a hand presented palm facing at 180 degrees is much easier than rotating a hand presented ‘side from thumb’ at 180 degrees. The ranks were established by two independent assessors and based on the RTs of participants in a pilot study (ranking is detailed in Table 5.3.1). The effect of Stimulation and Rank (1,2,3,4) on reaction time (RT) and accuracy were explored for each mental rotation task. During reaction time (RT) data analyses, inaccurate trials and RTs greater than three standard deviations from the mean were excluded. Where sphericity was not assumed, the Greenhouse-Geisser correction was used, and a Bonferonni adjustment was applied for multiple comparisons. Significance was defined with an alpha level below .05.

Table 5.3.1. Ranking of stimuli orientation for Experiment 1 of Study 4.

Orientations for each viewing position of hand and object stimuli for each task organised by difficulty ranking.

Difficulty Ranking	Orientation (degrees)								Object 3D V&K x & z
	Hand								
	Left		Right						
	Back	Palm	5 th Finger	Thumb	Back	Palm	5 th Finger	Thumb	
1	0	0	0	0	0	0	0	0	0
2	45, 90	45, 90	270, 315	45, 90	45, 270, 315	270, 315	270, 315	270, 315	45, 90, 270, 315
3	135, 270, 315	135, 315	45, 90, 225	135, 315	90, 225	45, 225	45, 225	45, 225	135, 225
4	180, 225	180, 225, 270	135, 180	180, 225, 270	135, 180	90, 135, 180	90, 135, 180	90, 135, 180	180

5.3.2. Results

Effect of stimulation on RT. Critically, stimulation did not significantly affect RT: Stimulation ($F_{(2,30)}=.064$, $p=.938$, $\eta_p^2=.004$), Task x Stimulation ($F_{(2,30)}=.282$, $p=.756$, $\eta_p^2=.018$), Stimulation x Rank ($F_{(3,348,50.221)}=1.053$, $p=.382$, $\eta_p^2=.066$), Task x Stimulation x Rank ($F_{(3,385,50.782)}=1.029$, $p=.394$, $\eta_p^2=.064$).

The remaining effects were not in relation to the modulatory effects of stimulation under investigation: a significant main effect was found for Task ($F_{(1,15)}=136.140$, $p<.001$, $\eta_p^2=.901$); participants were much slower when mentally rotating objects ($M=3235.521\pm1236.283$) compared to hands ($M=1474.883\pm484.504$). Furthermore a main effect of Rank ($F_{(1.846,27.695)}=116.578$, $p<.001$, $\eta_p^2=.886$) confirmed significant differences in RT across most ranks ($p<.05$); participants were significantly slower with increased mental rotation difficulty in all comparisons except between Rank 3 and Rank 4 ($p=.068$). Finally, a significant interaction

Task x Rank ($F_{(2.045,30.670)}=80.681, p<.001, \eta_p^2=.843$) was indicated. This interaction was not explored further as it was not related to the hypotheses.

Effect of stimulation on accuracy. A non-significant main effect of Stimulation ($F_{(2,30)}=.176, p=.840, \eta_p^2=.012$), and interactions Task x Stimulation ($F_{(2,30)}=.731, p=.490, \eta_p^2=.046$) and Stimulation x Rank ($F_{(3.714,55.713)}=.598, p=.653, \eta_p^2=.038$) were found. However a significant three-way interaction Task x Stimulation x Rank ($F_{(6,90)}=2.411, p=.033, \eta_p^2=.138$) was identified.

Two-way interactions were run to explore the significant three-way interaction, each time including Stimulation x Rank on each task individually. The interaction Stimulation x Rank was non-significant for the object mental rotation task ($F_{(6,90)}=1.092, p=.373, \eta_p^2=.068$), but significant for the hand mental rotation task ($F_{(6,90)}=3.876, p=.002, \eta_p^2=.205$). One-way ANOVAs examined the effect of stimulation at each difficulty ranking. A non-significant main effect of Stimulation was found when looking at Rank 1 ($F_{(2,30)}=1.522, p=.235, \eta_p^2=.092$), Rank 2 ($F_{(2,30)}=1.124, p=.338, \eta_p^2=.070$), and Rank 3 ($F_{(2,30)}=1.413, p=.259, \eta_p^2=.086$). However, a significant main effect of Stimulation was found for Rank 4 ($F_{(2,30)}=3.774, p=.035, \eta_p^2=.201$); pairwise comparisons revealed that accuracy was comparable between Sham ($88\% \pm 16$) and LPc/RPa ($90\% \pm 13$), $p=.868$, and between Sham and LPa/RPc ($86\% \pm 13$), $p=.558$. However accuracy was significantly greater during LPc/RPa compared to LPa/RPc, $p=.012$. It was anticipated that cathodal-inhibitory stimulation over the left parietal lobe would inhibit performance so this effect was unexpected (see Figure 5.3.2 for accuracy in both tasks). To establish whether the differences found between LPc/RPa and LPa/RPc are being driven by facilitation of the left hemisphere or inhibition of the right hemisphere (and vice versa), it is important to run a unilateral tDCS protocol.

Referring to the original three-way ANOVA the remaining effects were not in relation to the modulatory effects of stimulation under investigation. A significant main effect of Task ($F_{(1,15)}=18.344, p=.001, \eta_p^2=.550$) confirmed that participants were less accurate when mentally rotating objects ($M=87\% \pm 10$) compared to hands ($M=95\% \pm 7$). A main effect of Rank ($F_{(1.537,23.058)}=29.119, p<.001, \eta_p^2=.660$) indicated that accuracy reduced with increased difficulty of mental rotation; the difference in accuracy was significant in all comparisons ($p<.05$) except when comparing accuracy between Rank 3 and Rank 4 ($p=.063$). Finally a significant interaction Task x Rank ($F_{(1.888,28.317)}=12.962, p<.001, \eta_p^2=.464$) was indicated, but not explored as it was not directly related to the hypotheses. As in the case of effects on reaction times, this latter interaction arises from differences in task difficulty between the two tasks, and is of limited interest.

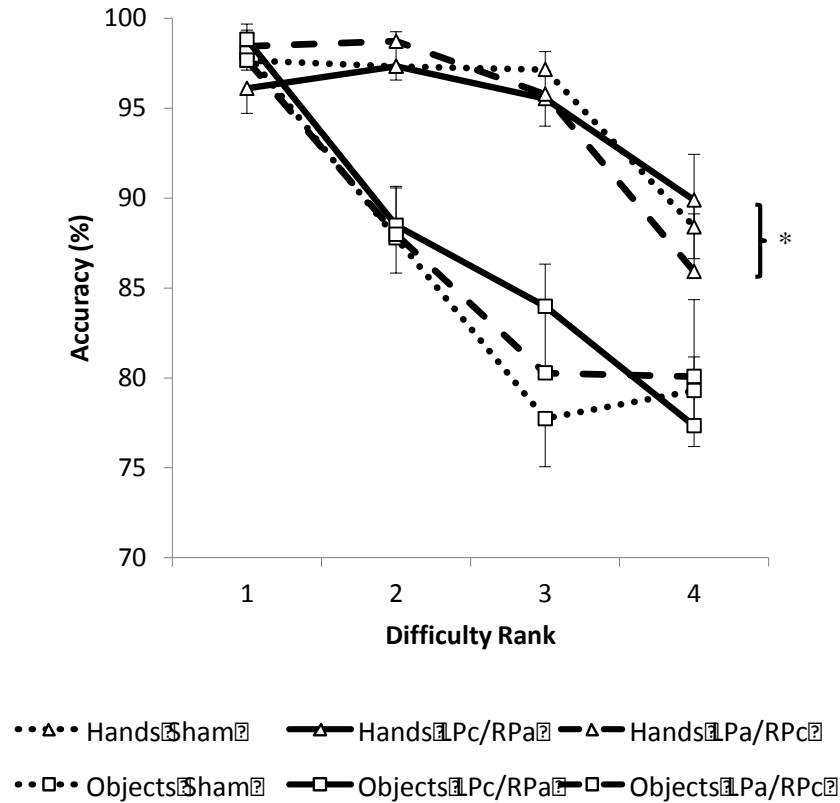


Figure 5.3.2. Response accuracy for Experiment 1 of Study 4.

Accuracy (%) for all participants, including standard error bars. Solid lines reflect left parietal cathodal-inhibitory and right parietal anodal-excitatory stimulation, dashed lines reflect left parietal anodal-excitatory and right parietal cathodal-inhibitory stimulation, and dotted lines reflect sham stimulation for both hand (triangles) and object (squares) mental rotation tasks. The asterisk marks the significant difference ($p=.012$) between LPc/RPa and LPa/RPc stimulation during hand mental rotation.

5.3.3. Discussion of Experiment 1

To shed light on the laterality debate of motor imagery, the effect of tDCS on mental rotation of hands and objects was explored. Across three sessions, electrodes were placed bilaterally over the parietal cortices, with either cathodal-inhibitory stimulation over the left parietal lobe while anodal-excitatory stimulation was applied to the right parietal lobe (LPc/RPa), anodal-excitatory stimulation over the left parietal lobe while cathodal-inhibitory stimulation was applied over the right parietal lobe (LPa/RPc), or sham stimulation. It was anticipated that if motor imagery was left hemisphere dominant, cathodal-inhibitory stimulation of the left parietal cortex would reduce reaction time and response accuracy when mentally rotating hands. As visual imagery is heavily right lateralised, it was also predicted that cathodal-inhibitory stimulation of the right parietal cortex would reduce reaction time and response accuracy during object mental rotation.

Exploring the effect of direct-current stimulation on task performance confirmed that cathodal-inhibitory stimulation over the left parietal lobe with anodal-excitatory stimulation over the right parietal lobe (LPc/RPa) enhanced response accuracy. Likewise, anodal-excitatory stimulation over the left parietal lobe with cathodal-inhibitory stimulation over the right parietal lobe (LPa/RPc) reduced response accuracy. Reaction times were not affected by stimulation.

Examining performance during hand mental rotation, both tDCS protocol affected response accuracy, but neither protocol affected reaction times. The effect of tDCS on response accuracy manifested when mentally rotating the most difficult hand orientations (Rank 4); response accuracy was enhanced during cathodal-inhibitory stimulation over the left parietal lobe with anodal-excitatory stimulation over the right parietal lobe (LPc/RPa) compared to reduced accuracy during anodal-excitatory stimulation over the left parietal lobe with cathodal-inhibitory stimulation over the right parietal lobe (LPa/RPc). Based on the implication of the left hemisphere during motor imagery (Haaland et al., 2004; Johnson-Frey et al., 2005; Muhlau et al., 2005), it is possible that the stimulation effect on performance accuracy was caused by modulation of the left parietal cortex. However, these modulatory effects were unexpected, as they did not adhere to the anticipated polarity effects of anodal and cathodal stimulation (i.e. excitatory and inhibitory respectively). As described by Jacobson and colleagues (2012) the inhibitory effects of left parietal anodal stimulation and excitatory effects of left parietal cathodal stimulation on task performance can be explained by the highly variable nature of tDCS during cognitive tasks. Depending on the duration and amplitude of stimulation, the anode and cathode have been shown to have the opposite polarity effects. Consequently, left parietal anodal stimulation may reduce accuracy during motor mental rotation and left parietal cathodal stimulation may improve accuracy.

Instead, it is also possible that the stimulation applied to the right hemisphere is driving the effect. As the current electrode montage does not allow the source of the stimulation effects to be teased apart (i.e. whether performance changes are driven by inhibition of the left hemisphere or excitation of the right hemisphere), a unilateral stimulation protocol was explored in Experiment 2; the target electrode was applied to the left or right parietal cortex while the reference electrode was placed over a neutral frontal reference site. That said it is important to note that task accuracy during both stimulation protocols were comparable to sham. Therefore it is likely that both protocols were having mild effects on task performance, which were only markedly different when compared to each other as opposed to compared to baseline performance. This suggests that motor mental rotation may rely on both motor and spatial processes from the left and right parietal cortices (Vingerhoets, de Lange, Vandemaele, Deblaere, & Achten, 2002).

The marginal and somewhat unpredicted stimulation effects on behaviour may be due to the stimulation sites being too close together. As reported in Wagner and colleagues (2007), there is a greater risk of “shunting” the electrical current over the scalp with increased electrode proximity, resulting in minimal stimulation penetrating cortical tissue. If this is the case, the current may be running over the surface scalp area instead of through the cortical regions of interest. The effect of shunting is of particular relevance to this task due to the bilateral parietal placement of electrodes. Specifically, there was a distance of approximately two to three centimetres between the electrodes, whereas to minimise the risk of shunting it may be more appropriate to separate electrodes by approximately eight centimetres (Wagner et al., 2007). As the current study was exploring the role of parietal regions in motor and visual imagery with bilateral stimulation, it was not possible to extend the distance between electrodes by much to reach the desirable separation between the electrodes.

Taking this into account, it cannot be determined whether one stimulation protocol was more effective than the other, given that performance during both protocols were comparable to sham. Likewise, due to bilateral tDCS electrode placement, it is uncertain whether accuracy was affected by modulation of the left or right parietal cortex. In other words, accuracy may have improved during left parietal cathodal-inhibitory and right parietal anodal-excitatory stimulation either due to the effects of the cathode on the left hemisphere, the effects of the anode on the right hemisphere, or a relationship between both left and right parietal stimulation (i.e. modulating the balance between parietal cortices). This also applies to the reduced performance found during left parietal anodal-excitatory and right parietal cathodal-inhibitory stimulation. Nevertheless, it can be concluded that placing the electrodes bilaterally over both parietal cortices may modulate performance accuracy during motor mental rotation tasks.

The lack of stimulation effects on reaction time may be due to task difficulty masking the effects of stimulation. If participants were responding slowly overall, it would be difficult to detect subtle changes in reaction time due to stimulation. Further, if participants try to maintain their response speed in more difficult trials, it might result in speed-accuracy trade-off compromising performance accuracy as opposed to speed. However this is speculative. Task difficulty may also explain why neither stimulation protocol (right parietal cathodal-inhibitory with left parietal anodal-excitatory or right parietal anodal-excitatory with left parietal cathodal-inhibitory) affected performance during the visual imagery control task, object mental rotation. Based on results indicating that object mental rotation is right lateralised (Corballis, 1997; Bricolo et al., 2000; Dong et al., 2000; Rumiati et al., 2001; Tomasino et al., 2003a; Tomasino et al., 2003b; Zacks et al., 2003a; Zacks et al., 2003b), it was anticipated that modulation of the right parietal cortex using tDCS would affect reaction time or accuracy performance during this task. Although

observable stimulation effects are expected when stimuli are presented in their most difficult orientations, reaction times during object mental rotation were considerably longer than hand mental rotation; on average participants took approximately three to five seconds to respond during object mental rotation compared to one and a half seconds when rotating hands. It is possible that participants are taking too long for the subtle stimulation effects to be observed. Likewise, the average accuracy during object mental rotation was approximately eight percent less than hand mental rotation. It may therefore be necessary to reduce task difficulty in order to confirm whether stimulation is affecting object mental rotation performance.

Based on the points listed above, it is important to explore the efficacy of obtaining a robust effect of direct-current stimulation during cognitive tasks exploring motor and visual imagery. Experiment 2 used different electrode montages to establish the optimum tDCS application to produce modulatory effects and to shed light on uncertainties highlighted in Experiment 1. In particular, given the unexpected effects of cathodal-inhibitory and anodal-excitatory stimulation in Experiment 1, the use of different electrode montages would indicate whether performance differences found here are driven by facilitation of the left hemisphere or inhibition of the right hemisphere (and vice versa). The stimuli used in the object mental rotation task were also changed.

5.4. Experiment 2: Exploring the efficacy of parietal tDCS in an imagery laterality task.

5.4.1. Method

Experiment 2 explored the efficacy of direct-current stimulation during mental rotation tasks using three different electrode montages. Given the unexpected effects of left parietal cathodal-inhibitory with right parietal anodal-excitatory stimulation having enhancing effects on task accuracy during hand mental rotation and the mild effects of tDCS on object manipulation perception in Study 2, this experiment hoped to shed further insight into the nature of the laterality effects found in Experiment 1. Further, it was hoped that an appropriate tDCS protocol could be established when examining cognitive laterality tasks implicating parietal regions. Assuming the classic polarity effects of tDCS, if motor imagery is left lateralised it was expected that cathodal-inhibitory stimulation of the left parietal cortex would reduce performance during hand mental rotation when one or more of the different electrode montages are applied.

Participants. A further opportunity sample of 37 ($M_{\text{age}} 21.5 \pm 8.0$, 21 female) right-handed participants (laterality quotient 76.93) was recruited using the same screening procedures as Experiment 1. Participants were divided into three separate studies that explored a specific electrode montage. Over two sessions, one participant group received the bilateral electrode

montage used in Experiment 1 but increasing the separation between the electrodes on each hemisphere to minimise the risk of shunting: cathodal-inhibitory and anodal-excitatory stimulation of the left and right parietal cortices ($N=10$). The other two groups received a unilateral stimulation protocol: one participant group received parietal cathodal-inhibitory and contralateral frontal anodal-excitatory stimulation ($N=13$), and a final participant group received parietal anodal-excitatory and contralateral frontal cathodal-inhibitory stimulation ($N=10$). Each group was analysed separately. Four participants were excluded from the final analyses for achieving an average accuracy $<70\%$.

Stimuli, design, and procedure. With the following exceptions, all aspects of the stimuli, design, and procedure were identical to those in Experiment 1. The sham condition was removed and a baseline condition was introduced prior to the main test block. During baseline participants completed each task without stimulation. This would increase the likelihood that participants are at optimum performance before stimulation is applied, reducing the risk of learning effects masking any effect of tDCS. The baseline block contained 12 practice trials and 40 experimental trials. After baseline, stimulation was then applied whilst participants completed the main test block for both tasks. Results for RT (ms) and accuracy (%) were analysed in the same way as Experiment 1 using Ranks.



Figure 5.4.1. Example of the 2D lamp box stimuli in Experiment 2 of Study 4.

As RTs in the object mental rotation task were much slower than the hand mental rotation task, the object stimuli were changed to stimuli that more appropriately matched the hand task. Instead of the 3D objects by Peters et al. (1995), participants were required to mentally rotate a two-dimensional (2D) 'lamp box' (see Figure 5.4.1 for example stimuli). Consistent with the hand stimuli, the lamp box was asymmetrical; the lamp had a light switch on one side in the same way that a hand has a thumb on one side. Unlike 3D objects, the lamp box therefore acts as a more comparable condition. After fixation a single lamp box appeared on screen and participants indicated whether the lamp box's light switch was on the left or right side of the object *if* the lamp box was facing forward. Participants pressed '3' with their right index finger if the light switch was on the right and '1' with their left index finger if the light switch was on the left. The lamp box was presented from a front and back position, and rotated clockwise from upright (0 degrees) in 45 degree increments, totalling eight orientations in each position. Orientations for the lamp

stimuli were ranked as described in Table 5.4.1. This task consisted of 96 trials where each stimulus condition was presented three times and had a short break in the middle.

Table 5.4.1. Ranking of stimuli orientation for Experiment 2 of Study 4.

Orientations for each viewing position of hand and lamp box object stimuli for each task organised by difficulty ranking.

Difficulty Ranking	Orientation (degrees)								Object 2D Lamp Box
	Hand								
	Left				Right				
	5 th				5 th				
	Back	Palm	Finger	Thumb	Back	Palm	Finger	Thumb	Front & Back
1	0	0	0	0	0	0	0	0	0
2	45, 90	45, 90	270, 315	45, 90	45, 270, 315	270, 315	270, 315	270, 315	45, 90, 270, 315
3	135, 270, 315	135, 315	45, 90, 225	135, 315	90, 225	45, 225	45, 225	45, 225	135, 225
4	180, 225	180, 225, 270	135, 180	180, 225, 270	135, 180	90, 135, 180	90, 135, 180	90, 135, 180	180

- i. Cathodal-inhibitory and anodal-excitatory stimulation of the left and right parietal cortices ($N=10$, 8 female).

Similarly to Experiment 1, the electrodes were placed bilaterally approximately over the IPL. To reduce the risk of shunting the centre of each electrode was placed between CP6 and P4, and CP5 and P3 (instead of CP4 and P4, CP3 and P3 used previously), extending the distance between the electrodes to 5-6cm. This was the furthest distance that the electrodes could be extended when stimulating the IPL in two separate sessions: receiving either LPc/RPa or LPa/RPc stimulation.

- ii. Unilateral parietal cathodal-inhibitory and frontal anodal-excitatory reference stimulation ($N=13$, 6 female).

Due to shunting remaining a risk with bilateral electrode placement, a more classic electrode montage was explored. Participants received parietal cathodal-inhibitory stimulation whilst the anode-excitatory electrode was placed over the contralateral supraorbital ridge, as a neutral reference site (Nitsche et al., 2008). The centre of the parietal electrode was placed between P3 and CP3 and P4 and CP4 in accordance with Harris & Minuissi's (2003) original electrode placement. Over two sessions, participants received left parietal cathode-inhibitory and right frontal anode-excitatory stimulation (LPc/RFa), and right parietal cathode-inhibitory and left frontal anode-excitatory stimulation (RPc/LFa).

- iii. Unilateral parietal anodal-excitatory and frontal cathodal-inhibitory reference stimulation ($N=10$, 7 female).

A final electrode montage explored the effect of anodal-excitatory parietal stimulation whilst the cathode-inhibitory electrode was placed over the contralateral supraorbital ridge as a reference site. Excitatory stimulation over the left and right hemisphere was used to investigate the possibility that there is an increased likelihood of getting excitatory effects of stimulation on cognitive tasks opposed to inhibitory effects (Jacobson et al., 2012). Over two sessions, participants received left parietal anode-excitatory and right frontal cathode-inhibitory stimulation (LPa/RFc), and right parietal anode-excitatory and left frontal cathode-inhibitory stimulation (RPa/LFc).

5.4.2. Results

- i. Cathodal-inhibitory and anodal-excitatory stimulation of the left and right parietal cortices.

Effect of stimulation on RT. A non-significant main effect of Stimulation ($F_{(1,9)}=1.060$, $p=.330$, $\eta_p^2=.105$), and interactions Task x Stimulation ($F_{(1,9)}=.068$, $p=.800$, $\eta_p^2=.008$), Stimulation x Rank ($F_{(2,0339,18,295)}=1.441$, $p=.262$, $\eta_p^2=.138$, and Task x Stimulation x Rank ($F_{(1,316,11,845)}=.017$, $p=.943$, $\eta_p^2=.002$) suggest that stimulation was not having an effect on RT (see Figure 5.4.3 for RT graph).

A main effect of Rank ($F_{(1,217,10,952)}=10.114$, $p=.007$, $\eta_p^2=.529$) confirmed that RTs increased when more mental rotation was required; RTs significantly decreased from Rank 1 to 2 ($p=.016$) and Rank 2 and 3 ($p=.006$) but were otherwise comparable ($p>.05$). A significant main effect of Task ($F_{(1,9)}=5.128$, $p=.049$, $\eta_p^2=.363$) indicated that participants were significantly slower when mentally rotating hands ($M=1160.743 \pm 167.210$) compared to objects ($M=988.905 \pm 182.405$).

Effect of stimulation on accuracy. Stimulation did not have a main effect on accuracy ($F_{(1,9)}=.229$, $p=.643$, $\eta_p^2=.025$) and the effect of stimulation did not differ between tasks: Task x Stimulation ($F_{(1,9)}=2.342$, $p=.160$, $\eta_p^2=.207$), Task x Stimulation x Rank ($F_{(3,27)}=1.111$, $p=.362$, $\eta_p^2=.110$). However, a significant interaction Stimulation x Rank was identified ($F_{(3,27)}=3.190$, $p=.040$, $\eta_p^2=.262$).

Post hoc analyses exploring the Stimulation x Rank interaction revealed a non-significant main effect of Stimulation for each Rank individually ($p \geq .141$), clarifying that it is not the case that the effect of stimulation manifests in the most difficult ranks. The Stimulation x Rank interaction appears to be driven by a complex interplay between rank order changes under the different

stimulation protocols in both tasks equally, as has been illustrated in Figure 5.4.2. However this is not related to the research questions and is not further explored.

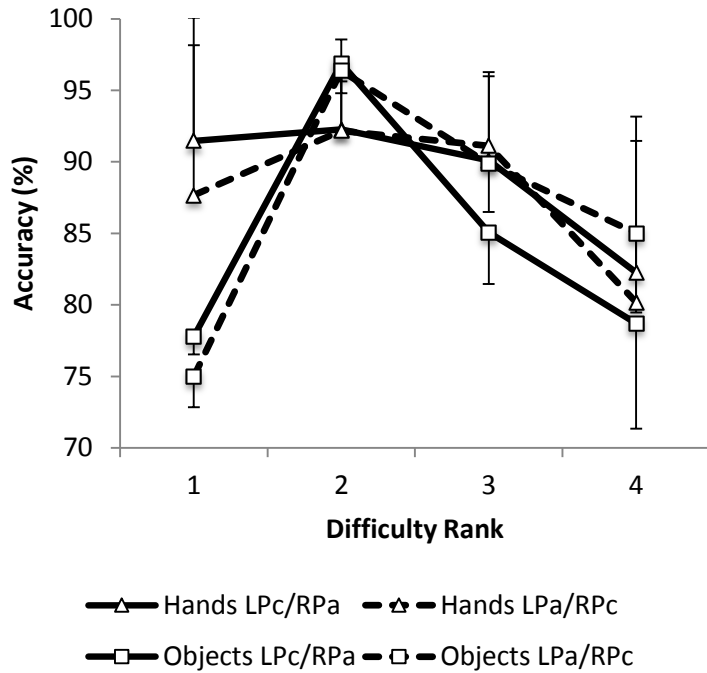


Figure 5.4.2. Response accuracy for LPC/RPa and LPa/RPc for Experiment 2 of Study 4.

Response accuracy (%) during left parietal cathodal-inhibitory and right parietal anodal-excitatory stimulation (and vice versa) for all participants, including standard error bars. Solid lines reflect left parietal cathodal and right parietal anodal stimulation, and dashed lines reflect left parietal anodal and right parietal cathodal stimulation for both hand (triangles) and object (squares) mental rotation tasks.

Referring to the original three-way ANOVA, the remaining effects were not in relation to the modulatory effects of stimulation under investigation. A non-significant main effect of Task ($F_{(1,9)}=1.089$, $p=.324$, $\eta_p^2=.108$) was found. Design related task difficulty generated a significant main effect of Rank ($F_{(1.774,15.987)}=15.669$, $p<.001$, $\eta_p^2=.635$). The interaction Task x Rank ($F_{(1.351,12.157)}=4.403$, $p=.012$, $\eta_p^2=.328$) was also found, however as it was not directly related to the hypotheses it was not explored. Figure 5.4.2 suggests the interaction was caused by the drop in accuracy when the stimuli are presented in the upright position of the object mental rotation task.

ii. Unilateral parietal cathodal-inhibitory and frontal anodal reference stimulation.

Effect of stimulation on RT. Non-significant main effect of Stimulation ($F_{(1,12)}=1.994$, $p=.183$, $\eta_p^2=.143$), and interactions Task x Stimulation ($F_{(1,12)}=.221$, $p=.647$, $\eta_p^2=.018$) and Task x

Stimulation x Rank ($F_{(3,36)}=.219$, $p=.883$, $\eta_p^2=.018$) were found. A significant interaction Stimulation x Rank ($F_{(3,36)}=3.569$, $p=.023$, $\eta_p^2=.229$) was explored (see Figure 5.4.3 for RT graph).

Post hoc analyses explored Stimulation x Rank by collapsing each task and comparing the effect of Stimulation on each rank individually. Although the effect of stimulation was not evident on the easier Ranks ($p \geq .230$), the interaction seems to be driven by the effect of stimulation on the reaction times on the most difficult stimuli (Rank 4) approaching significance ($p=.053$). This suggests that performance is affected by direct-current modulation when stimuli were more difficult to rotate. The means reveal that this effect is evident when parietal lobe processing is inhibited during the LPc/RFa protocol. Observing RTs, participants were slower during LPc/RFa ($M=1555.050 \pm 575.366$) compared to RPc/LFa ($M=1315.647 \pm 382.449$). These results therefore suggest that performance in both hand and object mental rotation tasks may have been marginally affected by left parietal cathodal-inhibitory stimulation when stimuli were more difficult to rotate.

Referring to the original three-way ANOVA on RT, the remaining effects were not in relation to the modulatory effects of stimulation under investigation. A significant main effect of Task was revealed ($F_{(1,12)}=7.684$, $p=.017$, $\eta_p^2=.390$); participants were slower completing the hand mental rotation task ($M=1294.288 \pm 180.418$) compared to the object mental rotation task ($M=1028.908 \pm 94.2148$). A significant main effect was also found for Rank ($F_{(1.407,16.878)}=34.594$, $p<.001$, $\eta_p^2=.742$); post hoc pairwise comparisons confirmed that RTs significantly decreased when required mental rotation increased for all Rank comparisons ($p<.05$) except between Rank 1 and Rank 2. Finally a non-significant interaction Task x Rank ($F_{(1.508,18.100)}=.621$, $p=.505$, $\eta_p^2=.049$) indicated that participants RT behaviour changed similarly in both hand and object mental rotation tasks.

Effect of stimulation on accuracy. Three-way ANOVA confirmed non-significant effects of stimulation on accuracy: Stimulation ($F_{(1,12)}=1.986$, $p=.184$, $\eta_p^2=.142$), Task x Stimulation ($F_{(1,12)}=.001$, $p=.974$, $\eta_p^2<.001$), Stimulation x Rank ($F_{(3,36)}=.181$, $p=.908$, $\eta_p^2=.015$), and Task x Stimulation x Rank ($F_{(3,36)}=.567$, $p=.640$, $\eta_p^2=.045$).

The remaining effects were not in relation to the modulatory effects of stimulation under investigation. A significant main effect of Task ($F_{(1,12)}=14.618$, $p=.002$, $\eta_p^2=.549$) confirmed that participants were more accurate during the hand mental rotation task ($93\% \pm 6$) compared to the object mental rotation task ($90\% \pm 6$). Main effect of Rank was also identified ($F_{(1.418,17.020)}=22.394$, $p<.001$, $\eta_p^2=.651$). Pairwise comparisons indicated that participants were significantly more accurate when mentally rotating stimuli at difficulty Rank 2 ($M=96\% \pm 4$)

compared to Rank 1 ($M=84\% \pm 5$) and Rank 3 ($M=94\% \pm 6$), but comparable compared to Rank 4 ($M=91\% \pm 10$). Performance also significantly improved from Rank 1 to 2 and 3.

The significant interaction Task x Rank ($F_{(1,900,22.796)}=63.197, p<.001, \eta_p^2=.840$) was also found, but was not explored as it did not directly apply to the hypotheses. As was seen in the previous study, the interaction is likely due to the considerable drop in accuracy when the stimuli are presented in the upright position of the Object mental rotation task ($M=75\% \pm 4$) compared to the Hand mental rotation task ($M=94\% \pm 5$).

iii. Unilateral parietal anodal-excitatory and frontal cathodal reference stimulation.

Effect of stimulation on RT. The initial three-way ANOVA revealed a non-significant main effect of Stimulation ($F_{(1,9)}=.088, p=.774, \eta_p^2=.010$) and non-significant interactions Task x Stimulation ($F_{(1,9)}=.073, p=.793, \eta_p^2=.008$), and Task x Stimulation x Rank ($F_{(3,27)}=1.319, p=.289, \eta_p^2=.128$). A significant interaction was however found for Stimulation x Rank ($F_{(3,27)}=3.090, p=.044, \eta_p^2=.256$).

Post hoc analyses of Stimulation x Rank with each task collapsed confirmed non-significant main effects of stimulation on RT for each rank separately ($p \geq .507$) indicating that RT did not greatly differ for each rank depending on the stimulation protocol applied. When analysing each stimulation protocol separately however, significant differences were found. For LPA/RFc ($F_{(1,327,11.942)}=26.904, p<.001, \eta_p^2=.749$) participants RTs significantly slowed linearly with increased rank. Changes in RT followed the same pattern in the stimulation condition RPa/LFc ($F_{(1,208,10.873)}=18.030, p=.001, \eta_p^2=.667$), however RTs did not differ significantly between Rank 3 and Rank 4. These results suggest that the interaction may have been driven by the greater RT differences between Rank 3 and 4 during left parietal excitation compared to the minor changes in RT between Rank 3 and 4 during right parietal excitation (see Figure 5.4.3 for RT graph).

The remaining effects the initial three-way ANOVA not in relation to the modulatory effects of stimulation under investigation are as follows. A significant main effect of Task ($F_{(1,9)}=30.336, p<.001, \eta_p^2=.771$) confirmed that participants were slower when mentally rotating hands (1147.370 ± 323.635) versus objects (837.475 ± 188.020). A main effect of Rank was also identified ($F_{(1,184,10.600)}=25.156, p<.001, \eta_p^2=.737$). Pairwise comparisons confirmed that participants RTs significantly increased linearly with increased difficulty of mental rotation for all comparisons except between Rank 1 and 2 ($p=1.0$). The interaction Task x Rank ($F_{(1,9)}=6.285, p=.002, \eta_p^2=.411$) was also significant, however this was not explored as it was not relevant to the hypotheses.

Effect of stimulation on accuracy. No significant effect of stimulation was found on accuracy: Stimulation ($F_{(1,9)}=.318$, $p=.587$, $\eta_p^2=.034$), Task x Stimulation ($F_{(1,9)}=.060$, $p=.812$, $\eta_p^2=.007$), Stimulation x Rank ($F_{(3,27)}=1.978$, $p=.141$, $\eta_p^2=.180$), Task x Stimulation x Rank ($F_{(3,27)}=1.477$, $p=.243$, $\eta_p^2=.141$).

The remaining effects were not in relation to the modulatory effects of stimulation under investigation: the main effect Task ($F_{(1,9)}=3.735$, $p=.644$, $\eta_p^2=.067$) and interaction Task x Rank ($F_{(1.441,11.526)}=2.159$, $p=.166$, $\eta_p^2=.213$) were non-significant. A significant main effect of Rank ($F_{(3,27)}=11.701$, $p<.001$, $\eta_p^2=.565$) was identified. Pairwise comparisons confirmed that accuracy significantly improved when comparing Rank 1 ($M=81\% \pm 7$) to Rank 2 ($M=93\% \pm 7$) and Rank 3 ($M=86\% \pm 9$), and between Rank 2 and Rank 4 ($M=83\% \pm 15$).

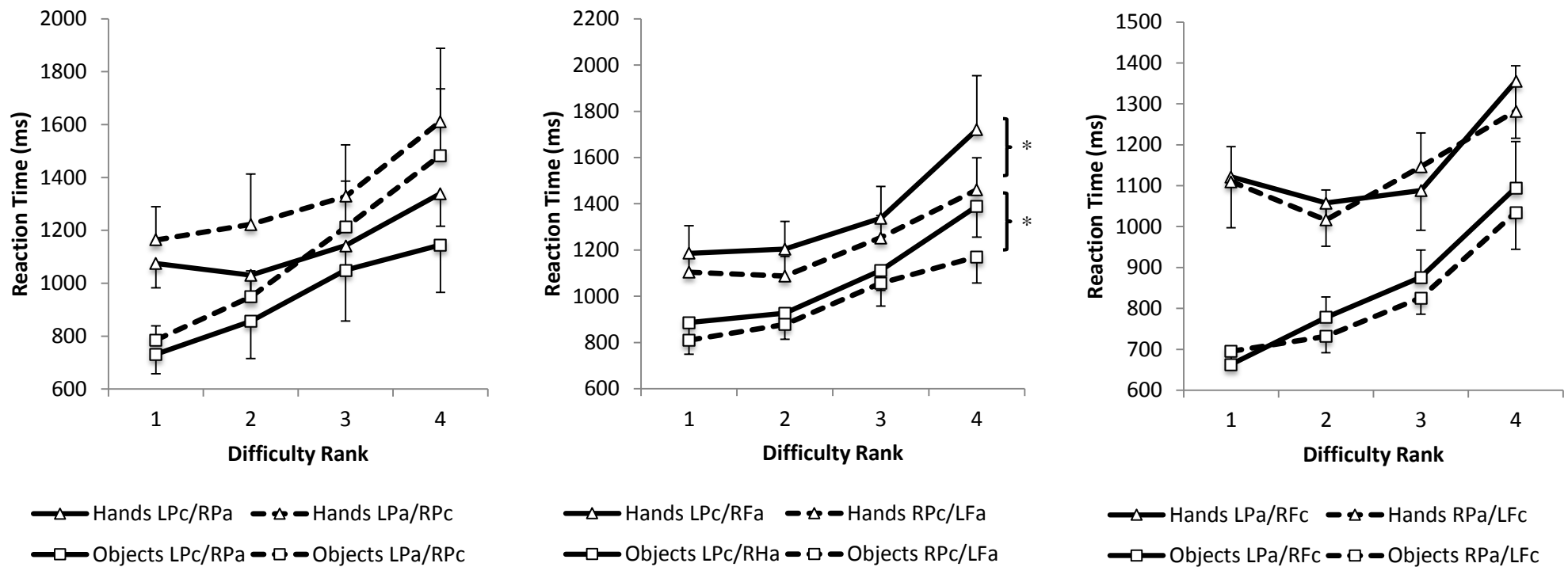


Figure 5.4.3. Reaction times for each electrode montage in Experiment 2 of Study 4.

RTs (ms) for all participants, including standard error bars. RTs are displayed at each rank during each stimulation session. Triangles reflect performance during Hand mental rotation and Squares reflect performance during Object mental rotation. (Left) Solid lines = Left Parietal cathodal-inhibitory and Right Parietal anodal-excitatory stimulation; Dashed lines = Right Parietal cathodal & Left Parietal anodal stimulation. (Middle) Solid lines = Left Parietal cathodal and Right Frontal anodal stimulation; Dashed lines = Right Parietal cathodal and Left Frontal anodal. (Right) Solid lines = Left Parietal anodal & Right Frontal cathodal stimulation; Dashed lines = Right Parietal anodal & Left Frontal cathodal stimulation. The asterisks mark the post hoc analysis trend $p=.053$ between LPC/RFa and RPa/LFa found for Rank 4 further to the significant interaction Stimulation x Rank.

5.4.3. Discussion of Experiment 2

By varying the electrode montages applied during tasks thought to evoke motor and visual imagery, Experiment 2 explored the efficacy of achieving modulatory effects of tDCS during cognitive mental rotation tasks. Three protocols were explored on separate participant groups: cathodal-inhibitory and anodal-excitatory stimulation of the left and right parietal cortices, unilateral parietal cathodal-inhibitory and frontal anodal-excitatory stimulation, and unilateral parietal anodal-excitatory and frontal cathodal-inhibitory stimulation. Modulation effects achieved by tDCS would also contribute to the laterality debate regarding motor and visual imagery. It was anticipated that if motor imagery is left lateralised, cathodal-inhibitory stimulation of the left parietal lobe would reduce hand mental rotation performance in one or more of the different electrode montages. Right parietal cathodal-inhibitory stimulation however was not expected to affect motor imagery.

Cathodal-inhibitory and anodal-excitatory stimulation of the left and right parietal cortices. Taking into account the risk of shunting the electrical current over the scalp (Wagner et al., 2007) the bilateral parietal electrodes were placed further apart to a distance of five to six centimetres between electrodes compared to two to three centimetres in Experiment 1. This was the maximal distance attainable whilst stimulating the cortical areas of interest. Comparable to Experiment 1, results confirmed an interaction between stimulation and rotation difficulty for accuracy but not reaction times. However stimulation modulated accuracy for both mental rotation tasks as opposed to the hand mental rotation task alone. Inspecting the differences in accuracy, results were inconclusive suggesting that performance change was largely driven by task difficulty as opposed to modulatory effects of stimulation. Although the electrodes were further apart, the distance remained less than the recommended eight centimetres, indicating that the risk of current shunting is still present (Wagner et al., 2007). However, given that modulatory effects were achieved in Experiment 1, it could be speculated that increasing the distance between the electrodes implicated different cortical networks to those in Experiment 1, potentially altering the effect of stimulation on task performance. Therefore using bilateral parietal placement of electrodes with increased distance is not the appropriate protocol for these tasks.

Unilateral parietal cathodal-inhibitory stimulation. A more traditional electrode montage was adopted by placing the cathode-inhibitory electrode over the parietal cortex and the anode-excitatory electrode over the contralateral supraorbital ridge as a reference. This protocol eliminated the risk of the direct-current shunting and allowed examination of left and right contribution to the effect to be disentangled now that we knew bilateral stimulation does not in fact generate enhanced effects. Unlike the bilateral parietal protocol in Experiment 1, parietal

cathodal-inhibitory stimulation decreased performance. Specifically, when mental rotation was most difficult (i.e. Rank 4) reaction times were considerably slower during stimulation of the left parietal cortex compared to the right. Unexpectedly, this effect occurred for both hand and object mental rotation tasks.

The results from unilateral parietal cathodal-inhibitory stimulation over the target site were consistent with the characteristic cathodal-inhibitory and anodal-excitatory polarity effects of tDCS. These stimulation effects corroborate those found in Study 2, where cathodal-inhibitory stimulation of the left IPL slowed reaction times during object manipulation perception. Conversely, in Experiment 1 of the current study, left parietal cathodal-inhibitory with right parietal anodal-excitatory stimulation improved accuracy during hand mental rotation, whereas left parietal anodal-excitatory with right parietal cathodal-inhibitory stimulation reduced accuracy during this task. The discrepancies in modulatory effects of bilateral parietal electrode placement observed in Experiment 1 and unilateral left parietal stimulation found here could be due to differences in current flow. Bilateral application of the electrodes transfers the direct-current through parietal regions, modulating the interaction between each hemisphere. According to Kinsbourne's (1977) theory of hemispheric rivalry, the parietal lobes compete to orient attention to the contralateral hemisphere. Application of TMS or tDCS over the left or right parietal lobes can disturb the interparietal balance of attention (Sparing et al., 2009). Similarly, bilateral parietal electrode placement in the current study might disturb the balance between hemispheres. Contrastingly, placement of one electrode over the parietal cortex and the other frontally over the contralateral supraorbital ridge transfers the direct-current through frontal and parietal regions. Recent reviews by Nitsche and colleagues (Nitsche et al., 2008; Nitsche & Paulus, 2011) confirm that the effects of tDCS vary significantly depending on the direction in which the direct-current is flowing. Therefore the contrasting polarity effects found in these experiments are likely because Experiment 1 is manipulating the interaction between the left and right parietal cortices whereas in Experiment 2 tDCS is having an isolated effect on the left or right parietal cortex.

However, because the sham condition during unilateral parietal cathodal-inhibitory stimulation in Experiment 2 was not repeated, it can of course not determine with full certainty whether reaction times slowed due to left parietal cathodal-inhibitory stimulation, or whether reaction times improved due to right parietal cathodal-inhibitory stimulation. The adjustment of the target electrode position to avoid shunting meant that the effects of this part of Experiment 2 were not the same as in Experiment 1. Assuming classic polarity effects are occurring, these findings support the proposal that motor imagery is left lateralised (Sirigu et al., 1996; Sirigu & Duhamel, 2001; Tomasino et al., 2003b; Haaland et al., 2004; Johnson-Frey et al., 2005; Muhlau et al., 2005; Overney et al., 2005; Overney & Blanke, 2009), however the role of this hemisphere during

visual imagery is unexpected. The comparable effect of tDCS on both mental rotation tasks is consistent with Pelgrims and colleagues (2009) who found that rTMS to the left or right parietal cortex affected mental rotation of hands and letters. Importantly, the effects of rTMS on performance differed depending on the specific region being stimulated; motor mental rotation was affected by stimulation of the supramarginal gyrus (SMG) whereas visual imagery was affected by stimulation of the superior parietal lobe (SPL). In the current study it may be possible that different forms of imagery are being used in each mental rotation task, but the flow of electrode current may be implicating both the SMG and SPL.

The design of the study was based on the premise that right hemisphere laterality of object mental rotation is fairly robust. Therefore the inhibitory effects of left parietal cathodal stimulation during this task were unexpected. Despite the proposed right parietal dominance for visual imagery, left hemisphere dominance during visual mental rotation has been hinted. Specifically, increased left parietal activity during mental rotation can depend on the type of the stimuli presented (Alivisatos & Petrides, 1997; Vingerhoets et al., 2001) and also the difficulty of mental rotation.

The isolated effect of left parietal stimulation on object mental rotation could also be attributed to the use of simplified two-dimensional objects. This is particularly evident in research exploring sex differences in mental rotation; males and females are suggested to rely on different parietal regions depending on the difficulty of mental rotation. During simple rotation of two-dimensional objects males rely on more left than right parietal activation and females more right than left parietal activation, whereas more complex three-dimensional stimuli lead to a comparable right parietal activation for both males and females (Blake et al., 2002; Roberts & Bell, 2003). Further, men show activation in the right parieto-occipital sulcus, left intraparietal sulcus and left superior parietal lobe (Jordan et al., 2002). By simplifying the objects from three- to two-dimensional stimuli the demand on right parietal regions may have been reduced. Therefore, both hemispheres may equally contribute to mental rotation of visual stimuli, with laterality effects emerging depending on the difficulty of mental rotation (Mellet et al., 1998; Jordan et al., 2001; Feredoes and Sachdev, 2006). However, it must be noted that the effects of stimulation on mental rotation were marginal and did not quite reach statistical significance in post hoc analyses.

Overall the current data tentatively confirms that unilateral left parietal cathodal-inhibitory stimulation with a frontal reference electrode impacts on cognitive performance during motor and visual mental rotation tasks, which support the results observed in Study 2. The modulatory effects caused by this electrode montage differ from those observed during bilateral parietal electrode placement in Experiment 1.

Unilateral parietal anodal-excitatory stimulation. As a final condition, the effect of unilateral parietal anodal-excitatory stimulation with a cathodal reference over the contralateral supraorbital ridge was explored. Based on the results found during unilateral parietal cathodal-inhibitory tDCS, it was anticipated that anodal-excitatory stimulation might have the opposite effect on task performance; anodal stimulation might enhance performance during mental rotation tasks. However, results instead indicate that this stimulation protocol had very little effect. Although an interaction was identified between stimulation protocol and mental rotation difficulty, further examination of participants' reaction times indicated that performance change was largely driven by difficulty rather than modulation. This supports the lack of excitatory effects of anodal stimulation during object manipulation perception in Study 2. Therefore, unilateral parietal anodal-excitatory stimulation is not an appropriate protocol to modulate performance during motor and visual mental rotation tasks or during object perception.

Combined with the results from Study 2, the lack of observable effects of anodal-excitatory tDCS during both mental rotation tasks suggests that Jacobson and colleagues (2012) proposal that facilitatory effects are more likely in cognitive tasks is overly simplistic at least with regards to the densely connected parietal lobes. It is possible that the likelihood of achieving either inhibitory or facilitatory effects of stimulation is task specific rather than dependent on whether the task is motor or cognitive in nature.

Exploration of the three electrode montages confirmed that modulatory effects of tDCS on performance during motor and visual mental rotation tasks are best achieved using unilateral left parietal cathodal-inhibitory stimulation with a frontal reference anode. By examining unilateral electrode montages, the results from Experiment 2 add insight into the modulatory effects observed in Experiment 1. Bilateral parietal electrode placement (Experiment 1) affects the interaction between the two parietal cortices, altering performance accuracy for the hand mental rotation task in isolation. Unilateral parietal tDCS on the other hand affects the left parietal cortex in isolation, modulating reaction times during both mental rotation tasks. Both protocols in Experiment 1 and 2 modulated performance during the most difficult mental rotation trials.

5.5. General Discussion

5.5.1. Laterality of motor and visual imagery.

Albeit weak, the results from both experiments confirm that motor imagery is left lateralised, in line with the findings of Study 1 and 2. Performance when mentally rotating hands was modulated

by cathodal-inhibitory and anodal-excitatory stimulation of the left and right parietal cortices (Experiment 1) and unilateral parietal cathodal-inhibitory stimulation (Experiment 2). Performance accuracy when mentally rotating the most difficult hand orientations was enhanced during left parietal cathodal-inhibitory with right parietal anodal-excitatory stimulation, and reduced during left parietal anodal-excitatory and right parietal cathodal-inhibitory stimulation. As accuracy during both stimulation protocols was comparable to sham it is assumed that both stimulation protocols were having an effect on performance. Contrastingly, unilateral left parietal cathodal-inhibitory stimulation slowed reaction times during difficult hand mental rotation. Despite the effects found for the bilateral parietal electrode montage leaving matters unclear with regards to a left or right parietal source of motor imagery, the unilateral inhibitory effect on the left parietal lobe brings converging evidence to suggest a left lateralisation for motor imagery.

This is consistent with the modulatory effects of Study 2, where response times during object manipulation perception were slowed when cathodal-inhibitory stimulation was applied to the left IPL. Neuroimaging data also confirms greater activation in the left parietal cortex during motor mental rotation (Bonda et al., 1995; Kosslyn et al., 1998; Haaland et al., 2004; Johnson-Frey et al., 2005; Muhlau et al., 2005; Overney & Blanke, 2009) and neuropsychological evidence shows a selective deficit in hand mental rotation when left parietal regions are compromised (Sirigu & Duhamel, 2001; Tomasino et al., 2003a; Tomasino et al., 2003b; Overney & Blanket, 2009).

Although the combination of Experiment 1 and 2 points in the direction of the left hemisphere lateralisation of motor imagery, Experiment 1 in isolation could suggest that the right hemisphere may be recruited. This is however not at odds with existing research. Supporting neurostimulation data from Pelgrims and colleagues (2009) confirms that rTMS over the left or right SMG disrupts hand mental rotation. Notably, the effects of both bilateral parietal electrode montages (left anodal and right cathodal versus left cathodal and right anodal tDCS) could be driven by modulation of the left hemisphere, right hemisphere, or by disrupting any interhemispheric interaction. Based on these findings, it can be concluded that motor mental rotation is left hemisphere dominant, but that right parietal regions may also be recruited.

Unexpectedly, unilateral parietal cathodal-inhibitory stimulation had the same effect on reaction time during object mental rotation; reaction times were slower during unilateral left parietal cathodal-inhibitory stimulation compared to right parietal cathodal-inhibitory stimulation. Despite a general assumption that visual imagery is right hemisphere dominant (Corballis, 1997; Pegna et al., 1997; Kosslyn et al., 1998; Tomasino et al., 2003b; Harris & Miniussi, 2003), the implication of bilateral or left parietal activation has been identified depending on the type of stimuli being rotated and task difficulty (Cohen et al., 1996; Alivisatos & Petrides, 1997;

Carpenter et al., 1999; Vingerhoets et al., 2001; Vingerhoets et al., 2002; Pelgrims et al., 2009). These results however conflict with neuropsychological data indicating that right parietal damage disrupts mental rotation of objects (Ditunno & Mann, 1990; Bricolo et al., 2000; Tomasino et al., 2003b). Unlike patient populations, as tDCS modulates the excitability of the stimulated neurons healthy participants are able to use compensatory mechanisms, interchanging between visual and motor strategies to complete the task. This is particularly an issue when either strategy is being disrupted by tDCS.

5.5.2. Efficacy of tDCS stimulation during mental rotation tasks.

Observing the results from both experiments in this study, and the results from Study 2 confirming mild modulatory effects of stimulation during the first test block only, it can be generally concluded that achieving parietal tDCS effects on cognitive performance is difficult. Overall, the most effective electrode montages were bilateral parietal electrode placement used in Experiment 1, and unilateral left parietal cathodal stimulation with a frontal anodal reference in Experiment 2. Both protocol modulated performance during the most difficult mental rotation trials, however notably each had a different effect on task performance. For the hand mental rotation task, left parietal cathodal-inhibitory with right parietal anodal-excitatory stimulation enhanced task accuracy compared to reduced accuracy during left parietal anodal-excitatory with right parietal cathodal-inhibitory stimulation. Alternatively, reaction times during both hand and object mental rotations were slowed with unilateral left parietal cathodal stimulation. Therefore cathodal stimulation was found to have both excitatory and inhibitory effects on performance. The remaining electrode montages, bilateral parietal electrode placement with increased separation between the electrodes, and unilateral parietal anode-excitatory stimulation with a frontal cathode reference did not show an effect of stimulation.

Although stimulation effects were found in two of the four electrode montages, these effects were very mild. There are several reasons why this may be the case. Exclusively to Experiment 1, as discussed, the proximity of each electrode increases the likelihood that some of the current is being shunted over the scalp reducing the intensity of stimulation penetrating the cortical tissue, thus reducing the effects of tDCS on cognitive function (Wagner et al., 2007; Nitsche et al., 2008). More generally, the nature of tDCS itself reduces the likelihood of finding observable effects of stimulation; unlike TMS that directly disrupts the neurons by causing an action potential, tDCS more subtly increases or decreases neuronal excitability. Consequently, it is possible to compensate for the modulatory effects of stimulation. Evidence of this may be seen in Study 2 where the effect present in the earlier part of stimulation disappeared in the latter part of stimulation duration. Similarly, if both motor and visual imagery recruit left and right parietal regions, the contralateral hemisphere to that being stimulated could compensate for the

modulatory effects of tDCS. Finally, by measuring reaction time and task accuracy, the effects of tDCS are highly susceptible to external noise (Jacobson et al., 2012). For example, despite counterbalancing of stimulation protocol and the use of sham and baseline conditions, by testing participants over multiple testing sessions means that learning is a large influence on the data patterns. In addition, large variance in task performance both within and between participants may be masking some of the effect of stimulation. Collectively, these points suggest it is possibly unrealistic to expect more than marginal effects when applying tDCS during similar cognitive tasks.

Evaluation of each electrode montage across both experiments highlighted key considerations when targeting parietal regions to assess cognitive functions using tDCS. Jacobson and colleagues (2012) indicated that it is inappropriate to assume anodal-excitatory and cathodal-inhibitory polarity effects of tDCS, particularly when examining cognitive functions. According to this review, both the anode and cathode have shown the opposite polarity effects depending on the duration and intensity of stimulation. Anodal stimulation was also considered more likely to modulate cognitive task performance. The current study supports and conflicts this theory; parietal cathodal stimulation both enhanced and disrupted performance during mental rotation tasks confirming the variable polarity effects of cathodal stimulation. However, unilateral anodal parietal stimulation failed to modulate performance on either task suggesting that it is incorrect to assume excitatory stimulation is more likely to affect cognitive task performance. Instead tDCS effects on performance may be task dependent.

It is also important to consider the direction in which the direct-current is flowing; depending on where the electrodes are placed on the scalp different effects of tDCS have been identified (Nitsche et al., 2008; Nitsche & Paulus, 2011). This is particularly important when considering the location of the reference site, or the use of bilateral or unilateral electrode montages. In this example, bilateral parietal electrodes isolate the current over posterior regions of the brain, whereas parietal and frontal electrode placement implicates posterior and anterior cortical regions. Each montage not only manipulates the regions of interest but any interactions between these areas through neuronal networks. Given the asserted role of both the left and right parietal cortices in mental rotation tasks, the effect of bilateral tDCS could be attributed to disruption in the interaction between hemispheres when calling on either motor or visual imagery, or both. Conversely, a unilateral electrode montage with a reference site does not affect the relationship between hemispheres. Therefore it is important to consider the interactions between different cortical regions when deciding where the electrodes are placed on the scalp.

Together, these results confirm that with certain electrode montages tDCS can modulate performance during mental rotation tasks. Modulation of hand mental rotation performance is easier to achieve than object mental rotation where performance was only affected by unilateral parietal cathodal-inhibitory stimulation, but not in the expected right hemisphere. These results also emphasise the importance of exploring different electrode montages when evaluating the effect of tDCS during cognitive tasks. Experimental findings and stimulation protocol should be described in detail, including duration, intensity, electrode positioning and the direction of current flow.

In conclusion, based on the modulatory effects of tDCS during Experiment 1 and 2, it can be confirmed that motor imagery shows left hemisphere dominance during hand mental rotation. However, the laterality of visual imagery, although intended as a control condition, was less clear. Firstly, as visual mental rotation was affected by only one of the four electrode montages, modulation of visual imagery is harder to achieve, although the inclusion of visual imagery in this study was intended as a robust and relatively well established as a right hemisphere process. Secondly, the effect of tDCS on object mental rotation appears to largely depend on task requirements. Moreover, the current data emphasise the difficulties that can be faced when exploring the effect of tDCS, particularly on cognitive tasks. Specifically, these experiments highlight the importance of reporting tDCS stimulation parameters in detail. As few studies being conducted using unilateral parietal or bilateral electrode placement during cognitive mental rotation tasks, the current study confirms that successful stimulation effects can be achieved. Therefore it is important to build on the current findings in future research in order to further understand how direct current stimulation affects cortical activity.

Chapter 6

General Discussion

Overall the results from the studies described in this thesis suggest that apraxia may be attributed to impaired internal movement representations. The selective deficits of apraxic patients not only appear restricted to the motoric elements of action, but also manifest during skilled movement requiring integration of perception for action. These behaviours thereby support the notion of an additional ventro-dorsal sub-stream of the visual pathways model. By integrating causal techniques from neuropsychology and neuromodulation, the results of this thesis also support the integral role of the left IPL in generating and maintaining these motor representations. In this general discussion, the findings from each empirical study shall be described. These findings will then be discussed in relation to the key questions that this thesis set out to answer: whether apraxia is attributed to impaired internal movement representations (i.e. motor imagery) due to damage to a purported ventro-dorsal stream, and whether these internal movement representations are reliant on maintained processing within the left inferior parietal lobe (IPL). The discussion will be concluded with possible future directions that can be taken from these results.

6.1. Summary

Using a newly devised perceptual task, Study 1 assessed whether object-use errors in left hemisphere stroke patients with apraxia are restricted to motoric elements of object-use. A critical distinction was made between motoric manipulation judgements of how objects are grasped for use (e.g. how a hammer is held) and non-motoric functional semantic judgements of how two objects are used together (e.g. how a hammer hits a nail). If apraxia is attributed to impaired motor imagery, errors were expected to be restricted to motoric action representations. Results confirmed that apraxic patients made considerably more errors when perceiving hand-object interactions in the manipulation condition when compared to healthy age-matched control participants. Comparable performance between apraxic patients and healthy age-matched controls in the semantic screening tasks and functional semantic condition of the experimental task confirmed that errors in the manipulation condition could not be attributed to semantic or object processing deficits. A correlation with the severity of apraxia confirmed that poor performance in the manipulation condition but not in the functional semantic condition was associated with more severe apraxia. The selective deficit of apraxic patients during object manipulation perception strongly supports the proposal that apraxia is associated with impaired

internal representations of movement, or motor imagery, due to disruption to a proposed ventro-dorsal stream. Examining lesion data, approximately half of the patients with apraxia had lesions directly encompassing the left IPL whereas the remaining apraxic patients had lesions involving other regions of the frontoparietal motor network including the cerebellum, thalamus, broca's area, and underlying white matter. Although not directly damaged in these patients, it remains possible that the left IPL is indirectly disturbed due to disrupting communication between different parts of the ventro-dorsal pathway. Together, lesion data indicate that internal movement representations may indeed be reliant on maintained processing within the left IPL.

Study 2 used the relatively novel neuromodulation technique tDCS with healthy participants to directly assess the role of the left IPL in motor imagery and the ventro-dorsal stream, building on lesion data from Study 1. Using a modified version of the perceptual task used in the previous study, two experiments were run with different participant groups to assess the effects of left parietal cathodal-inhibitory or anodal-excitatory stimulation on task performance. If the left IPL is critical during motor imagery, modulation of this region should selectively affect manipulation perception. In Experiment 1, participants received cathodal-inhibitory stimulation over the left IPL with a frontal reference electrode. Compared to sham, results confirmed that stimulation increased reaction times when participants made object manipulation perceptual decisions. However, stimulation effects were only present in the first of two test blocks suggesting participants compensated for stimulation effects over time. A separate participant group in Experiment 2 confirmed no effects of stimulation during the manipulation condition when anodal-excitatory stimulation was applied over the left IPL with a frontal reference electrode. Neither cathodal-inhibitory nor anodal-excitatory parietal stimulation affected performance during functional semantic decisions in both experiments. The selective disruption of object manipulation perception with maintained functional semantic perception during cathodal-inhibitory tDCS causally confirms the proposal that internal movement representations are reliant upon processing in the left IPL adding weight to the lesion data found in Study 1. These results support the role of the left IPL in the integration of perceptual and action processes via a purported ventro-dorsal stream that may be disrupted in apraxia. However, the effects of tDCS on manipulation perception were not robust.

Expanding on data from Study 1 and 2 suggesting that ventro-dorsal disruption can impact manipulation perception for familiar objects, Study 3 examined whether apraxia impacts the ability to learn skilful manipulation of novel objects. A newly created action execution task indicated that when repeatedly lifting and balancing unevenly weighted cylindrical objects, a majority of apraxic patients failed to incorporate high-level visual affordance (visual dot) and memory-associated (object colour) cues of weight distribution. Grasp location were inaccurate

during repeated lifts and when the objects were reintroduced in later trials. A third patient with apraxia seemed to compensate for these difficulties. Alternatively, grasping behaviour of all apraxic patients was appropriate when weight distribution was cued by low-level visual affordances of the object shape (symmetrical cylinder) suggesting the traditional dorsal stream of the visual pathways model is intact. Further, apraxic patients who performed poorly in the high-level visual affordance and memory-associated conditions maintained central grasp-points regardless of weight distribution, indicating that preserved dorsal processing may bias grasp choice towards those visually afforded by the object's shape. Contrastingly, left hemisphere stroke patients without apraxia and healthy age-matched control participants successfully incorporated low-level visual affordance, high-level visual affordance, and memory-associated cues of weight distribution during repeated grasps and when the objects were reintroduced in later test blocks. Together, these results indicate that ventro-dorsal disruption can impair the use of familiar objects, but also predict that apraxia is associated with difficulty learning to skilfully manipulate new objects when low-level visual affordance cues do not correspond to appropriate functional grasps.

Based on the accumulated findings from the previous studies suggesting that the ventro-dorsal stream is indeed disrupted in apraxia, the final empirical Study 4 extensively explored the neuromodulation technique tDCS in healthy participants. Using classic hand and object mental rotation tasks shown to evoke motor and visual imagery respectively, the laterality of internal movement representations, and more specifically the role of the left IPL were assessed. As tDCS is a novel technique in imagery research coupled with its variable nature during cognitive tasks and lack of robust effect on manipulation perception in Study 2, different electrode montages were explored to assess the efficacy of modulating motor imagery. In Experiment 1, left parietal cathodal-inhibitory with right parietal anodal-excitatory stimulation improved accuracy during hand mental rotation, whereas left parietal anodal-excitatory and right parietal cathodal-inhibitory stimulation reduced accuracy in this task. Stimulation effects were found when the stimuli were at the most difficult orientations. Notably, performance differences were identified when comparing each stimulation protocol to each other; when each stimulation protocol was compared to sham, performance did not greatly differ. It was therefore assumed that both protocol were having a mild effect on hand mental rotation performance. Object mental rotation however was not affected by either stimulation protocol. In Experiment 2 three separate groups of participants were given one of three different electrode montages. The group receiving unilateral left parietal cathodal-inhibitory stimulation with a contralateral neutral frontal reference electrode showed slowed response times in the hand and object mental rotation tasks during the most difficult stimuli orientations when compared to right parietal cathodal-inhibitory stimulation with a frontal

reference. Remaining electrode montages did not markedly affect performance during either mental rotation task for the remaining participant groups.

The differing effects of stimulation in Experiment 1 and 2 suggest that bilateral parietal electrode placement impacts the interhemispheric interaction between parietal lobes, whereas unilateral parietal cathodal-inhibitory electrode placement affects the parietal lobe being stimulated in isolation. Therefore tDCS effects can vary depending on where the electrodes are placed. Albeit weak, the results from both experiments of Study 4 confirm that modulation of the left IPL impacts motor mental rotation performance. Supporting Study 2, these results suggest the left IPL is critical during motor imagery and indeed left lateralised. The unexpected effect of left parietal cathodal stimulation on visual mental rotation in Experiment 2 indicates the laterality of visual imagery is less clear. Although intended as a control condition, modulation of object mental rotation is harder to achieve with tDCS.

6.2. Is apraxia attributed to impaired motor imagery due to a disrupted ventro-dorsal pathway?

The general introduction of this thesis described how apraxia has come to be considered an impairment in the generation and maintenance of internal representations of movement, or motor imagery, due to disruption to a purported ventro-dorsal pathway. One of the main aims of the current thesis was to assess this claim by using a combination of action perception and action execution tasks with left hemisphere stroke patients with apraxia. These tasks were designed to carefully dissect the processes that are preserved and lost in these patients. As internal movement representations are necessary during motor execution and simulation, the integrity of these representations can be assessed in apraxia using tasks requiring motor imagery. Focusing on skilful use of objects, in order to confirm whether apraxia is attributed to impaired motor imagery, errors must be specific to the motoric elements of object-use. If this is the case, for these deficits to be attributed to disruption to the ventro-dorsal pathway, errors in object-use should be confined to skilled movement where perceptual information must be integrated into action plans, whilst traditional ventral processing of semantic representations and dorsal processing of online object manipulation based on affordance remain intact. Both studies with apraxic patients (Study 1 and 3) offer direct evidence in support of these claims. The tasks devised in these studies expanded on previous research by assessing both action perception and execution of object-use behaviour in apraxia that has seldom been explored; equivalent performance errors across action perception and execution tasks with familiar and novel objects offers an evaluation of apraxia's relationship with movement representations in the ventro-dorsal pathway from input (perception) to output (execution).

6.2.1. Familiar object-use

Focusing on the use of familiar objects, the selective deficit in object manipulation perception observed in Study 1 suggest that apraxia may be attributed to impaired motor imagery resulting in deficient perception of the motoric elements of object-use. The proposal that apraxia may be attributed to disrupted internal representations of movement stems from examination of the core symptoms of apraxia. Deficits appear to be confined to skilled movement, impacting action execution and action perception. During gesture imitation, apraxic patients show defective performance when imitating gestures performed by a model (Haaland & Flaherty, 1984; Haaland et al., 2000; Buxbaum et al., 2005; Buxbaum et al., 2007), and failure to produce meaningful gestures on command such as the symbolic action “how to salute” or object-use pantomime including “how to use a hammer” (Goldenberg, 1995; Buxbaum, 2001). In severe cases, errors during object pantomime extend into actual object-use, for example patients may use the wrong tool-object combination such as attempting to cut bread with a spoon (Goldenberg, 2013). Similar deficits have been reported for action perception; apraxic patients fail to recognise pantomimed actions or identify their own actions from those performed by others (Rothi et al., 1985; Sirigu et al., 1999). Further, case study data suggest performance is reduced during mental chronometry after parietal damage (Sirigu et al., 1995; Sirigu et al., 1996) and performance during the hand laterality judgement task is also impaired (Tomasino et al., 2003a; Tomasino et al., 2003b; Overney & Blanke, 2009). What these symptoms have in common is that they relate to gestural based skilled movement. In addition to assessing whether apraxic errors are restricted to motoric elements of action, it is important to confirm more explicitly whether these errors manifest only when the appropriate motor response is reliant on integration of perception for action.

To verify whether apraxic errors are restricted to skilled movement implicating motor imagery via the ventro-dorsal stream, the components of object-use were carefully dissected to evaluate what functions disturbed and maintained in these patients. Research suggests that apraxic patients have maintained ventral processing; patients can successfully recognise and identify visually presented objects (Daprati & Sirigu, 2006), and organise familiar objects in weight order (Dawson et al., 2010; Li et al., 2011). These semantic representations were also intact in a majority of apraxic patients in Study 1; patients were able to identify target objects and the object typically used with that target based on verbal command. When pairing objects that share a similar function (for example a matchstick and a lighter both make a flame) in the presence of distractor items, apraxic patients also perform appropriately (Buxbaum & Saffran, 2002; Myung et al., 2010), confirming that representations of the functional purpose of familiar objects are maintained. In studies evaluating the integrity of representations of object function and manipulation participants are typically required to match pictures or words of objects in isolation. Tasks such as these do not tease apart the actions required by both the objects and the actor to achieve that goal. It

therefore remained possible that patients with apraxia can identify the function of the object, but not the motion required to fulfil that function (e.g. the head of the hammer must move in a downward motion onto the object being hit). Study 1 of this thesis not only explored the integrity of object manipulation perception in apraxia but also non-motoric functional semantic representations of how an object is used to fulfil its functional purpose, confirming that these non-motoric action representations are undisturbed. Together, maintained semantic, function, and functional semantic representations indicates that perceptual representations attributed to the ventral stream are intact in apraxia. Likewise, the inclusion of affordance-related distractor items in each condition of Study 1 is evidence that accurate performance in semantic and functional semantic conditions could not be attributed to affordance cues allowing appropriate target selection based on the structure of each object.

Instead, errors manifest when performing the actions associated with object-use; Study 1 confirmed that apraxic patients were impaired when matching the appropriate manipulation gesture for familiar objects and that these errors increased with the severity of apraxia. These gestural based errors add weight to previous research suggesting that apraxic patients perform abnormally when matching familiar objects that are similarly manipulated (De Renzi & Lucchelli, 1988; Buxbaum & Saffran, 2002; Buxbaum et al., 2005; Rumiati et al., 2004; Vingerhoets et al., 2008; Myung et al., 2010) or when recognising the correct hand posture required for skilled object-use (Buxbaum et al., 2003; Daprati et al., 2010). Therefore, the selective deficits when retrieving motoric representations of object-use, whilst non-motoric action representations are maintained, confirm that object representations are distributed across the brain. These errors also suggest that apraxia is strongly related to disruption of what Goldenberg calls the “cognitive side” of motor control (Goldenberg, 2009; Goldenberg, 2013).

6.2.2. Novel object-use

The errors observed in apraxia also extend to the skilful use of novel objects. Importantly, very few studies have assessed whether apraxic patients can learn to skilfully manipulate new objects, which may also be reliant on internal representations of movement to assess whether the movement plan will achieve the action goal. Study 3 confirmed that apraxic patients generally perform poorly with new objects, even with increasing experience over time. A majority of the patients with apraxia failed to accommodate for the weight distribution of the objects when it was indicated by a high-level visually afforded cue or a memory-associated cue. In other words, grasp errors manifested when it was necessary to integrate the visual cue of object weight from the ventral stream with dorsal processing of object shape and location. Impaired application of perception for action in apraxia has also been observed during object-based problem solving tasks; patients fail to select the tool best suited to manipulate a cylinder during the novel tools test

(Goldenberg & Hagmann, 1998; Goldenberg & Spatt, 2009), perform a sequence of object-based manipulations to open a mechanical puzzle (Heilman et al., 1997), or use familiar objects in an unusual way such as screwing a screw with a knife (Osiurak et al., 2009; Sunderland et al., 2011). The selective deficits of apraxic patients during skilled object-use in Study 3 support the perceptual errors demonstrated in Study 1; stored representations of object function must be incorporated into the action plan in order to select the appropriate object manipulation gesture. Combined, these results indicate that motor perception and execution are disturbed in apraxia when visible and known properties of objects must be integrated via the ventro-dorsal stream.

Alternatively, object manipulation was unaffected when weight distribution was indicated by low-level visual affordance cues of object structure, confirming that apraxic patients could perform adequately on the basis of maintained dorsal processing (i.e. when motor imagery was not required to assess the appropriateness of the movement plan to achieve the action goal via the ventro-dorsal stream). Although few studies have explored apraxic patients performance when learning to manipulate novel objects, these results support those that have been conducted. Barde and colleagues (2007) trained patients to match novel gestures to novel objects that were high or low afforded by their associated objects. Patients with apraxia showed an affordance benefit during action recognition, performing appropriately to control participants when the gesture was highly afforded to the object shape. However, performance was poorer compared to controls when the gesture and object affordance was low. Like Study 3, apraxic patients showed a performance advantage when the appropriate grasp gesture could be inferred from the shape of the object. These selective deficits correspond to evidence that performance errors reduce with increased contextual information; during pantomime, demonstration, and actual object-use, pantomime was prone to the most errors, whereas performance improved with increasing perceptual cues (Randerath et al., 2011). Similarly, during imagined or actual grasping of dowels and widgets presented in varying orientations, apraxic errors were markedly worse during the imagery condition where there was minimal visual, tactile, and proprioceptive feedback, as opposed to action execution where there is strong visual feedback (Buxbaum et al., 2005).

Not only do the results from Study 3 support the suggestion that motor imagery is impaired in apraxia, but also confirms that traditional dorsal processing is maintained in these patients. This is corroborated by patients' ability to infer the function of novel objects and accurate grasping of objects for transfer (Sirigu et al., 1995; Goldenberg & Hagmann, 1998; Buxbaum et al., 2003; Ietswaart et al., 2006; Randerath et al., 2009; Randerath et al., 2010; Sunderland et al., 2013). Likewise, maintained semantic, functional, and functional semantic representations confirmed in the literature and in Study 1, indicates that traditional ventral processing is preserved in apraxia (Daprati & Sirigu, 2006; Dawson et al., 2010; Li et al., 2011). Therefore, close examination of

object-use behaviour in apraxia confirms that performance errors cannot be attributed to impaired ventral or dorsal streams of the traditional visual pathways model (Goodale & Milner, 1992; Milner & Goodale, 2006). Instead, these results suggest that object manipulation deficits in apraxia are restricted to actions where perceptual information must be incorporated into action plans, therefore supporting the existence of a ventro-dorsal sub-stream of the visual pathways model that utilises stored representations to enable objects to be grasped for skilled action (Rizzolatti & Matelli, 2003; Buxbaum & Kalénine, 2010; Binkofski & Buxbaum, 2013; Vingerhoets, 2014). Failure to access and implement information from the ventral stream into action plans results in an over-reliance on intact dorsal processes, resulting in objects being manipulated based on their visual affordance regardless of the goal of the action (Randerath et al., 2011).

Notably, during repeated lifts of familiar and novel objects apraxic patients have been shown to successfully adjust their grip force, appropriately demonstrating a maintained ability to utilise sensorimotor feedback (Gordon et al., 1993; Hermdörfer et al., 2011; Randerath et al., 2011; Eidenmüller et al., 2014). Despite this behaviour supporting the proposal that apraxic patients can use short-term information to update movement plans via the dorsal stream, Study 3 did not show improved grasp performance over repeated lifts of the same objects in a majority of apraxic patients. However it is believed that these behaviours are not attributed to impaired sensorimotor feedback. In Study 3 the visual affordance cues of object weight, suggesting an even weight distribution due to being a symmetrical cylinder, are in conflict with sensorimotor feedback that indicates that the object is weighted to the left or the right in the high-level visually-afforded or memory-associated conditions. Consequently, the results from Study 3 suggest that apraxic patients may fail to adapt their behaviour if the visual affordance cues do not correspond to the appropriate functional grasp. In studies assessing grip force rather than grasp-point, the visual shape of the object does not conflict sensorimotor feedback of object weight. The presence of performance errors in Study 3 therefore raises an interesting question: if action is biased towards intact visual affordance cues due to disturbed ventro-dorsal processing in apraxia, can these patients effectively utilise intact short-term nonvisual processes (i.e. sensorimotor feedback) if these do not correspond to visual information? In addition to this question, by testing additional apraxic patients lesion analysis may indicate that performance is maintained when certain cortical regions or white matter tracts are preserved. Further, modification of the task design, such as incorporating a delay before grasp onset, would confirm whether compensatory techniques could be utilised to improve performance.

Nevertheless, through a unique assessment of action perception and action execution, Study 1 and 3 strongly support the proposal that apraxia is associated with impaired internal movement

representations due to disruption to the ventro-dorsal pathway. In accordance with the literature, accurate performance in the semantic and functional semantic conditions of Study 1 confirm that ventral processing is intact in these patients, whilst accurate performance in the low-level visual affordance condition of Study 3 indicates that dorsal processing is preserved. Apraxic errors therefore cannot be attributed to damage to either stream of the traditional visual pathway model. Conversely, a selective impairment when making perceptual decisions regarding the skilful manipulation of familiar objects in Study 1 confirms that errors are motoric in nature, suggesting motor imagery is indeed impaired. When combined with inaccurate grasping of novel objects when stored representations must inform action plans in Study 3, results highlight that these errors are not only motoric, but confined to actions reliant on the integration of perception for action attributed to the ventro-dorsal pathway. Through careful evaluation of object-use errors in apraxia, Study 1 and 3 offer substantial support the presence of a ventro-dorsal pathway that is impaired in apraxia in a manner that has not been tested previously. Disturbance of this pathway affects the perception and execution of skilful action for both familiar and novel objects.

6.2.3. Is apraxia attributed to impaired mechanical problem solving?

In the general introduction of this thesis, the proposal that apraxia is attributed to impaired mechanical problem solving was described. According to Goldenberg and colleagues (Goldenberg & Hagmann, 1998; Goldenberg, 2013), the theory of disturbed object manipulation perception implied the existence of prototypical gesture representations for individual objects that are stored and retrieved. As discussed in the introduction, the notion of a core gesture representation is flawed for several reasons. Instead, it is more plausible that the motor representations required for appropriate object manipulation and potentially impaired in apraxia are attributable to a flexible high-level praxis system. Yet the question remains as to whether apraxia can be attributed to impaired mechanical problem solving. Goldenberg and colleagues suggested that apraxic patients fail to identify the functional capabilities of objects in order to plan a movement to effectively achieve the movement goal. Identification of the capabilities of an object requires long-term stored movement representations to be generated to assess whether the planned movement will achieve the goal, which would also require the integration of the ventral and dorsal systems. This theory therefore not only accounts for errors during novel and familiar object-use, but a deficit in mechanical problem solving might also be attributed to impaired motor representations via the ventro-dorsal pathway.

Reviewing the errors observed in apraxia, it is argued that mechanical problem solving does not truly represent apraxic behaviour. Crucially, Goldenberg argues that mechanical problem solving applies equally to movements and configurations of external objects and the body; functional representations associate the “types of tools with their purpose, their recipient, and the action of

their use” (Goldenberg, 2013, p. 121). Conversely, these have been shown to be distinct in previous research; semantic, function, and manipulation perception can be selectively impaired (Boronat et al., 2005; Buxbaum & Saffran, 2002; Canessa et al., 2008; Myung et al., 2010). In particular, Goldenberg proposed that left parietal lesions impair comprehension of the spatial relationship between multiple objects, multiple parts of objects, and between the hand and the object (Goldenberg, 2009). However, when the perception of spatial relationships between multiple objects was assessed in apraxia (Study 1) and when applying tDCS to the left IPL in healthy populations (Study 2), functional semantic representations were maintained. These findings indicate that apraxic errors emerging from left parietal damage cannot be attributed to impaired comprehension of the mechanical relationships between external objects, which contradicts Goldenberg’s claim. Secondly, although impaired mechanical problem solving can be applied to action execution errors when skilfully manipulating familiar and novel objects such as during the novel tools test, it is less clear how it can be applied to errors in object-use pantomime. When pantomiming the use of objects, particularly in response to verbal command, affordance cues regarding the functional capabilities of the object are not readily available. Therefore, it might be more appropriate to suggest that instead of the proposal of storehouses of prototypical object-use gestures as Goldenberg assumes, there may be the presence of simpler motor “primitives” that are represented as combinations of critical features that are retrieved and modified depending on task demands (Schenk, 2014). Based on apraxic patients behaviour in the studies of this thesis and with support from the literature, it seems more reasonable that skilled object manipulation is reliant on the integration of short- and long-term visual representations that are generated depending on the goal of the motor act. However, the question of mechanical problem solving versus high-level motor representations remains a topic of intense debate.

6.3. Do internal representations of movement rely on maintained processing within the left inferior parietal lobe (IPL)?

Although the results from Study 1 and 3 offer substantial support for the proposal that apraxia is attributed to impaired motor imagery due to disruption to the ventro-dorsal pathway, what was less clear was the role of the left IPL. The introduction of this thesis outlined research from both neuroimaging and neuropsychology that suggests the left IPL is the critical juncture where ventral and dorsal processing is combined, forming a fundamental part of the purported ventro-dorsal pathway (Rizzolatti & Matelli, 2003; Buxbaum & Kalénine, 2010; Rizzolatti et al., 2011). However, the role of the left IPL has been questioned, in particular during object-related movement (for example Goldenberg et al., 2007). Using causal neuropsychological and neuromodulation techniques, the second aim of this thesis was to confirm whether internal movement representations attributed to the ventro-dorsal stream are reliant on intact processing within the left IPL. By assessing the necessity of the left IPL in tasks calling upon motor imagery,

it could also be inferred whether it is accurate to suggest these representations are compromised in apraxia.

Lesions to frontal and parietal regions of the visuomotor network often lead to apraxia, with the left IPL being consistently associated with ideomotor apraxia (Haaland et al., 2000; Leiguarda & Marsden, 2000; Goldenberg, 2009). Study 1 and 3 corroborated these findings, as approximately half of the apraxic patients tested had lesions that directly implicated the left IPL, suggesting that damage to this region can affect skilful object manipulation. Lesions to the left IPL have been associated with impaired imitation of hand gestures and with errors during pantomime and actual object-use (Goldenberg & Spatt, 2009; Goldenberg, 2014). However, errors in gesture recognition and pantomime of object-use is also apparent when lesions occur outside of the parietal lobe; reduced understanding of familiar transitive and intransitive gestures and disturbed pantomime of object-use has been associated with disruption to frontal regions including the inferior frontal gyrus, but not damage to inferior parietal regions (Goldenberg et al., 2007; Pazzaglia et al., 2008; Bolthalter et al., 2011). These findings challenge the necessity of the left IPL during motor imagery, particularly during the mental simulation of object-related action.

However, as lesions are often extensive, it cannot be ruled out that the left IPL is indirectly implicated in these patients; if lesioned areas include corticocortical and corticosubcortical connections, communication along the ventro-dorsal pathway may still be disrupted (Leiguarda, 2001; Lewis, 2006). This issue was acknowledged in research associating frontal lesions with impaired object-use. Referring to Study 1 and 3, the patients with lesions external to the left IPL had damage extending into the underlying white matter of frontoparietal regions, and subcortical lesions including the cerebellum, thalamus, and broca's area. It is therefore possible that the reciprocal connections between the ventral and ventro-dorsal pathway, or the forward projections from parietal to frontal regions, are disconnected. Consequently it remains that the left IPL may be critical during motor imagery. Yet this explanation is not definitive and does not account for theta-burst stimulation over the inferior frontal cortex of healthy participants impairing production of transitive and intransitive gestures, while left IPL stimulation did not affect gesture production (Bolthalter et al., 2011).

Despite apraxic patients in Study 1 and 3 having lesions that may directly or indirectly implicate the left IPL, the causal link between the integrity of this region and maintained motor imagery via the ventro-dorsal stream remained unclear. Using tDCS, Study 2 and 4 assessed the role of the left IPL in greater depth. Any performance changes in motor imagery tasks due to modulating the cortical excitability of the left IPL would heavily reinforce its role in the integration of perception for action. When given the same perceptual task used with apraxic patients in the initial study,

healthy participants in Study 2 showed increased reaction times during the perception of object manipulation when left parietal cathodal-inhibitory stimulation was applied with a contralateral frontal reference electrode. As performance during functional semantic judgements was unaffected by stimulation, these findings confirm that the left IPL is required during the perception of motoric elements of object-use but not when perceiving non-motoric action representations. This corresponds to neuroimaging studies indicating that simulation of object-related movement activates several visuomotor areas attributed to the ventro-dorsal stream including the left IPL when individuals observe, imagine, and pantomime object-use (Chao & Martin, 2000; Decety et al., 2002; Mozaz et al., 2002; Rizzolatti & Matelli, 2003; Vingerhoets, 2008; Króliczak & Frey, 2009; Vingerhoets et al., 2009; Caspers et al., 2010). Increased left IPL activation is also observed when making perceptual based decisions and prospective action judgements regarding appropriate object-use, which can be disturbed after rTMS is applied to this area (Buccino et al., 2001; Kellenbach et al., 2003; Buccino et al., 2004; Rizzolatti & Craighero, 2004; Boronat et al., 2005; Buxbaum et al., 2006; Canessa et al., 2008; Ishibathi et al., 2011; Wadsworth & Kana, 2011). Alternatively, perception of object function activates inferotemporal regions, with impaired function judgements manifesting after damage to temporal regions in the case of semantic dementia or herpes encephalitis (Sirigu et al., 1991; Buxbaum et al., 1997; Bozeat et al., 2000; Kellenbach et al., 2003; Mahon & Caramazza, 2003; Boronat et al., 2005; Negri et al., 2007; Canessa et al., 2008). Such research suggests that functional semantic representations may similarly be attributed to more ventral and semantic systems.

The necessity of the left IPL during motor imagery is reinforced by the results found in Study 4. This study used classic mental rotation tasks that have consistently been shown to rely on motor or visual imagery depending on task demands (Bonda et al., 1995; Corballis, 1997; Overney et al., 2005; Overney & Blanke, 2009). During left parietal cathodal-inhibitory and right parietal anodal-excitatory stimulation accuracy of hand mental rotation was enhanced compared to left parietal anodal-excitatory and right parietal cathodal-inhibitory stimulation, indicating that disturbance of interhemispheric interactions between the parietal lobes could modulate motor imagery. Reaction times were also reduced during unilateral left parietal cathodal-inhibitory stimulation with a contralateral frontal reference. Unilateral right parietal cathodal-inhibitory or anodal-excitatory stimulation did not affect motor mental rotation performance. Unlike a previous rTMS study that found stimulation of the left or right supramarginal gyrus affected hand laterality performance (Pelgrims et al., 2009), the modulatory effects found in Study 4 are consistent with evidence that apraxic symptoms predominantly occur after damage to the left hemisphere. This suggests that motor imagery is left lateralised but may recruit right parietal regions that are supplementary but not essential (Sirigu et al., 1996; Buxbaum et al., 2005; Niessen et al., 2014). Further, the selective impairment of manipulation judgements during tDCS of the left IPL

confirms that additional frontal and white matter disruption is not necessary to disturb object-use perception as deduced by Vingerhoets and colleagues (2011).

Combined, the findings from both experiments in Study 4 indicate that modulation of the left IPL affects intransitive motor mental rotation. Similarly to object-related movement, several ventro-dorsal visuomotor areas, in particular left parietal regions, are active during the mental rotation of body parts (Bonda et al., 1995; Kosslyn et al., 1998; Rizzolatti & Matelli, 2003; Haaland et al., 2004; Fogassi & Luppino, 2005; Johnson-Frey et al., 2005; Muhlau et al., 2005; Overney et al., 2005). In accordance with neuroimaging data, impaired motor mental rotation is observed when lesions implicate the left parietal regions (Sirigu et al., 1996; Sirigu & Duhamel, 2001; Tomasino et al., 2003a; Tomasino et al., 2003b; Overney & Blanke, 2009), whereas right parietal damage has been shown to impact visual mental rotation whilst motor mental rotation remains normal (Bricolo et al., 1990; Rumati et al., 2001; Tomasino et al., 2003b).

Overall, the results from Study 2 and 4 directly attribute the left IPL with the perception of transitive object-related action and intransitive mental rotation of hand gestures, corroborating a wealth of neuroimaging and neuropsychological data implicating the left IPL in transitive and intransitive movement (Decety et al., 1994; Decety, 1996; Sirigu et al., 1996; Rizzolatti & Craighero, 2004; Rumati et al., 2004; Lewis, 2006; Frey, 2007; Vingerhoets et al., 2008; Kalénine et al., 2010; Niessen et al., 2014). These results support the proposal of an additional sub-stream of the visual pathways model important for the integration of perception for action. Further, the lack of effect of tDCS when the right hemisphere was stimulated indicates that motor imagery is left hemisphere dominant. The modulatory effects of tDCS also compliment the lesion data from Study 1 and 3 that suggests direct or indirect disturbance of the left IPL is associated with deficits during the perception and execution of skilled object-related movement. That said, regions external to the left IPL, such as the right parietal lobe or inferior frontal gyrus, may still be integral to internal movement representations via the ventro-dorsal stream, but for different reasons. For example, while the left IPL might form the critical juncture where perception and action are integrated to enable the generation and selection of the appropriate movement gesture, it is feasible that the production of this gesture and inhibition of inappropriate gestures calls upon inferior frontal regions (Decety et al., 1997; Goldenberg et al., 2007). Overall, the results obtained from the neuromodulation studies confirm that when tDCS is applied to the parietal cortex, motor imagery can be modulated. To date, this has seldom been explored and therefore offers unique evidence for the potential of tDCS to assess the cognitive aspects of motor control. Importantly, these studies offer direct evidence for the role of the left IPL during skilled movement representations via the ventro-dorsal sub-stream.

6.4. What is the role of motor imagery and the left IPL?

Although accumulated results from the studies conducted in this thesis point to impaired internal movement representations due to disruption of the ventro-dorsal stream, it remains unclear what the role of these representations are. If apraxia is an example of the errors that can manifest when motor imagery is disturbed, what has been learned about the purpose of these movement representations?

The general introduction indicates that motor imagery is required during implicit or explicit movement simulation (Annett, 1995; Lotze & Halsband, 2006), and forms an important part of motor planning for action execution (Jeannerod & Decety, 1995; Mulder, 2007). Based on the data from this thesis it is likely that these representations are vital in generating and assessing the appropriateness of movement plans to achieve an action goal (Buxbaum et al., 2005; Goldenberg, 2009). Disturbed generation and assessment of these action plans results in inappropriate perception or production of transitive or intransitive gestures. As observed in the current data, impaired action planning results in inaccurate perception of the appropriate gesture for manipulating familiar objects, and impaired selection and execution of a suitable grasp, or grasp-point, when performing skilled object manipulation. These representations are not required to assess the appropriateness of action plans when movement can rely on the online control of action, for example when grasping objects based on their structural properties based on dorsal processing. Likewise, it is not necessary to refer to these representations when identifying an object and its typical function, which instead relies on semantic systems via the ventral stream. Therefore, it is possible that motor imagery forms a critical part of action selection by accumulating different information from motor, perceptual, and semantic systems in order to select the appropriate action in the given context.

If this is the case, it is plausible that the left parietal cortex, in particular the left IPL, is the region at which this information is combined. Anatomically situated between dorsal and ventral pathways (Rizzolatti & Matelli, 2003; Binkofski & Buxbaum, 2013), as part of the ventro-dorsal stream the left IPL is ideally placed to integrate information from these pathways. Whether this region is a modality-specific “spoke” of a larger semantic system (Lambon Ralph, Sage, Jones, & Mayberry, 2010; Ishibashi et al., 2011) or whether it is a central point where information is combined to form these internal representations remains uncertain. What is certain however is that the left IPL is critical in enabling information from the ventral and dorsal streams to inform action plans.

6.5. Conclusions and future directions

The studies in the current thesis offer a detailed assessment from input (perception) to output (execution) of the integrity of internal movement representations in apraxia and the role of the left IPL in generating these representations. In order to confirm whether motor imagery is compromised in apraxia, it was important to comprehensively assess several aspects of motor control, from action perception to action execution. It was also essential to assess whether the errors that manifest during the perception of familiar object-use are equivalent during the use of novel objects; if apraxia is to be considered an impairment in internal movement representations attributed to the ventro-dorsal pathway, errors were expected to manifest not only when perceiving the skilful manipulation of familiar objects, but also during skilful action execution with novel objects where long-term stored movement representations were required to inform action. The results from work with apraxic patients confirm that performance errors manifest during the retrieval of motor representations associated with learned, familiar objects and also impact the ability to learn skilful manipulation of new objects.

Particularly novel is that apraxia impacts learning of new objects, with short-term sensorimotor information failing to be utilised when visual and sensorimotor feedback are in conflict. To date very few studies have assessed how apraxia impacts learning; if apraxic patients struggle to learn how to skilfully manipulate new objects for example this will have a vast impact on their independence post-stroke and should be accounted for when determining the appropriate treatment of apraxia. Further, by using control tasks that examined the integrity of traditional dorsal and ventral streams of the visual pathways model, maintained functional semantic perception and object manipulation based on low-level visual affordances of object shape emphasise that the errors observed in apraxia could not be attributed to damage to either of these visual streams. Maintained performance in these conditions confirms that apraxic errors manifest not only during the motoric stages of object-use, but exclusively when ventral and dorsal processing must be integrated. This supports the suggestion of a ventro-dorsal sub-stream within the visual pathways model required when integrating perception for action. The use of lesion analysis and the neuromodulation technique tDCS also confirmed the necessity of the left IPL in skilled movement reliant on motor imagery. This region has been heavily implicated in the ventro-dorsal stream and in apraxia, adding a wealth of support for the suggestion that the left IPL forms the critical juncture where dorsal and ventral processing is combined.

Building on the data obtained in this thesis, it would be beneficial to expand on the novel grasping task used with apraxic patients. As described, few studies have explored how apraxia affects patients' ability to learn skilful manipulation of new objects. Therefore the results from the current grasping task raise some interesting questions that have not previously been explored,

emphasising the need to assess apraxic patients behaviour during learning. Expanding on the current data would also bring further insight into how perception and action processes interact. For example, modification of the study design such as incorporating a delay before grasp onset might reveal why some patients, like JA in this instance, can compensate for their deficits while others cannot. Likewise, it is possible that preservation of certain cortical regions or white matter tracts may allow improved performance. It is important to consider whether the integrity of these deeper cortical pathways is critical when integrating perception for action. Finally, it would be interesting to assess how sensorimotor information is incorporated into action plans; it may be possible that disturbing the ventro-dorsal pathway also prevents successful utilisation of nonvisual information when it is in conflict with visual affordance cues.

Future studies should also explore further stimulation protocol to obtain robust tDCS effects on motor imagery and assess the dissociable effects of tDCS when modulating parietal regions in isolation and the interhemispheric interaction between parietal lobes. Not only would this inform models regarding the functional purpose of the left IPL, but also whether there is an important relationship between the parietal lobes as suggested by the interhemispheric interaction effect of tDCS on motor imagery observed in Study 4. Finally, achievement of excitatory modulatory effects of tDCS during motor imagery would expand the role of this technique from an investigative technique towards developing its potential as a neurorehabilitation technique.

Together, the studies in this thesis confirm the existence of a ventro-dorsal stream that is critical in the perception and execution of skilled use of familiar and novel objects. Compromising this pathway impairs internal representations of movement resulting in errors during the perception and generation of transitive and intransitive gestures. This pathway can be impaired through direct disturbance of the left IPL or indirectly through disruption along the pathway disconnecting forward projections from parietal to frontal regions along ventro-dorsal network.

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