VISUOMOTOR DEFICITS IN POSTERIOR CORTICAL ATROPHY

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Abstract

Posterior Cortical Atrophy (PCA) is a rare clinical syndrome characterised by the predominance of higher-order visual disturbances. Deficits result from a progressive neurodegeneration of occipito-temporal and occipito-parietal cortices. Due to its relative scarcity, many common symptoms of PCA, such as visuomotor dysfunction, have yet to be fully investigated. The current study sought to explore the visuomotor abilities of four individuals with PCA by testing their ability to reach out and grasp real objects under various viewing conditions. The patients demonstrated many of the same deficits as those seen in individuals with optic ataxia, including impaired grip scaling to peripheral targets, poor selection of stable grasp sites, and evidence of 'magnetic misreaching' – a pathological reaching bias towards the point of visual fixation. Unlike individuals with pure optic ataxia, however, the patients in the current study showed symptoms indicative of damage to the ventral stream of visual processing, including abolished grip scaling during memory-guided grasping and an inability to differentiate objects based on their shape. This research increases our understanding of the visuomotor deficits associated with PCA. It also adds to our knowledge of how visual information is processed in the brain, including the complex interaction between vision for action and vision for perception.

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Visuomotor Deficits in Posterior Cortical Atrophy

In 2008, we were contacted by a woman, RB, who told us she was having trouble recognising people she had known for most of her life. She recounted a story of being at an art show and having an in-depth conversation with a woman for quite some time. It was only later revealed to RB that this was an old friend of hers with whom she had shared a studio for many years. RB also told us how she had great difficulty identifying family members in photos of a recent family gathering, and how she once talked to her son at a hockey game – only later realising that it was not her son she had been talking to. She did not report any difficulty recognising objects, memory issues, or having trouble finding her way around town. As she discussed these difficulties, we began to wonder if perhaps she was demonstrating pure prosopagnosia, a selective deficit in face recognition. However, just as our conversation was drawing to a close, she mentioned that sometimes when she closed her eyes and opened them again, the "world was a different colour". At this point, it became clear to us that this woman's issues were more complex than a specific inability to recognise faces – something else was going on.

We invited RB to our lab. During her first visit, we discovered that she exhibited a far more extensive set of deficits than she had informed us; more extensive, in fact, than she was even aware. We confirmed that her perceptual ability for faces was indeed disturbed, as she correctly identified only 1 out of 50 faces on a famous face recognition task. This deficit was not due to memory issues, as RB could talk very intelligibly about most of the famous people in our battery. What's more, her perceptual awareness of these faces was drastically impaired – more than a simple inability to combine the facial features into a perceptual whole. For example, when shown a picture of late-night television host, David Letterman, she asked, "Is that Michelle

Obama?" Clearly, RB was failing to correctly identify the gender or even the skin colour of these faces. Not surprisingly, her perceptual problems did not end with faces. When asked to identify simple line drawings of everyday objects, RB performed very poorly; she seemed unable to take in the 'big picture', focusing on small, individual aspects of an image and guessing at the object's identity based these few cues. For example, when shown a black-and-white image of a camera, she asked us if it was a tunnel – focusing on the tunnel-like appearance of the camera's lens. Furthermore, RB's colour 'hallucinations' were quite pervasive. When asked to identify the colour of our lab's whitewashed walls, she said they appeared green, and she reported the presence of many different colours in basic black-and-white images.

What was causing this myriad of visual impairments? RB hadn't experienced any recent head trauma, nor did she exhibit symptoms indicative of a stroke. RB's memory for the onset of her symptoms was good, she spoke cogently and intelligently, and she retained insight into her situation; the hallmarks of typical Alzheimer's disease were not present. What, then, were we dealing with?

Since our first encounter with RB, she has been diagnosed with Posterior Cortical Atrophy. Sometimes referred to as a "visual variant of Alzheimer's disease", Posterior Cortical Atrophy is a sparsely known, relatively understudied syndrome, and is the focus of this investigation.

Background

Posterior Cortical Atrophy

Posterior Cortical Atrophy (PCA) is a rare clinical syndrome characterised by prominent higher-order visual dysfunction. It results from progressive cortical neurodegeneration that

primarily targets occipital, posterior parietal, and posterior temporal cortices. This localised loss of neurons in areas of the brain responsible for visual processing means that patients with PCA suffer from a variety of visual symptoms such as alexia, agnosia, and optic ataxia. The cellular loss seen in this disorder is progressive, and PCA ultimately leads to dementia and death.

PCA is a relatively modern diagnosis. In 1985, Cogan presented three patients with poor or blurred vision, spatial disorientation, agnosia, and alexia without agraphia. He concluded that these visual disturbances were an atypical early presentation of Alzheimer's Disease (AD), and proposed that visuospatial tests be included in diagnostic batteries for AD. Three years later, Benson, Davis, and Snyder (1988) described five more patients with similar symptoms. Benson's patients all showed progressive mental deterioration and early visual dysfunction. Importantly, they demonstrated no basic motor or sensory abnormalities, and both visual acuity and visual field sensitivity remained intact until late in the disorder. One of the earliest complaints made by each patient was disorientation and getting lost in familiar situations, such as the local neighbourhood or around their own house. As the disorder progressed, four of Benson's patients demonstrated complete Balint's syndrome (defined by Benson as: sticky fixation, ocular dysmetria, and simultanagnosia), with the fifth showing the two symptoms for which he was tested – sticky fixation and ocular dysmetria. Furthermore, all five patients met the criteria for full Gerstmann's syndrome (finger agnosia, right-left disorientation, agraphia, and acalculia) and transcortical sensory aphasia (indicated by anomia, alexia, and agraphia, with impaired comprehension and intact repetition). Benson's patients also shared the presence of visual agnosia and constructional apraxia; only minor memory impairments until late in the disorder; and the retention of considerable insight into their situation.

Benson and colleagues (1988) performed computed tomography (CT), magnetic resonance imaging (MRI), and an electroencephalogram (EEG) on all five of their patients. EEGs revealed a similar pattern of activity to that seen in the mid-stages of both AD and Pick's disease. Importantly, however, the anatomical scans revealed a different pattern of regional degeneration from AD and Pick's disease, with the presence of predominant occipito-parietal atrophy in three of the cases. Based on the results of CT, MRI, and angiograms, Benson and colleagues were able to discount three possible pathological causes of these symptoms: a disconnect of intact primary visual cortical areas from various association cortices, demyelination, and focal vascular disease.

Benson, Davis, and Snyder provided a list of clinical findings that distinguished their patients' diagnoses from those of typical Alzheimer's (tAD) or Pick's disease. Firstly, patients with PCA and tAD show an early onset of constructional apraxia, environmental agnosia, and acalculia – symptoms which are only seen late in Pick's disease. Secondly, alexia, agraphia, and Gerstmann's syndrome all appear relatively early in PCA, while these same symptoms appear at a moderately late stage in both tAD and Pick's disease. Furthermore, Balint's syndrome – a common result of PCA – is rarely seen in tAD or Pick's disease. Finally, unlike patients with tAD or Pick's disease, patients with PCA show well preserved insight and appropriate self-concern until late in the disorder. Despite this evidence, the authors conceded that it was possible their patients exhibited an atypical presentation of AD or a "posteriorally localized variant of Pick's disease" (Benson et al., 1988). However, based on the similarities in the course, the presence and combination of symptoms, and the location of cortical atrophy, Benson suggested a novel diagnosis – Posterior Cortical Atrophy.

PCA is a gradually progressive disorder with an insidious, often presenile onset (Mendez, Ghajarania, & Perryman, 2002; Zakzanis & Boulos, 2001). Common initial complaints of patients with PCA include difficulties reading, writing, and performing simple calculations. Patients often describe having trouble driving, getting dressed, and seeing or recognising objects in front of them. Reports of blurred vision and getting lost in familiar surroundings are also frequent. Somewhat less common complaints include hallucinations, colour disturbances, a partial loss of vision, and mild memory loss. However, it is important to note that memory deficits are almost always overshadowed by prominent visual dysfunction (McMonagle, Deering, Berliner, & Kertesz, 2006).

Memory, insight, and judgement are generally well preserved in patients with PCA until later in the course of the disorder, at which point these faculties may begin to diminish (Benson et al., 1988). On average, the progressive neurodegeneration seen in PCA leads to dementia five years following the onset of symptoms (Schmidtke, Hüll, & Talazko, 2005), and the life expectancy for patients with PCA is eight to 12 years (Croisile, 2004). Of course, there is a large degree of inter-patient variation in the course of the disorder, and dementia and death may not occur for much longer in some individuals.

Since Benson's initial identification, a debate has raged among researchers and clinicians about whether PCA is indeed a distinct neurological entity, or simply a variant of another more common disease (Mendez et al., 2002; Tang-Wai & Mapstone, 2006). While this argument is far from over, a strong case has been made in recent years in favour of PCA being recognised as a unique disorder (McMonagle et al., 2006; Tang-Wai et al., 2004). Currently, PCA does not have an entry in either the DSM-IV-TR or the ICD-10, so official diagnostic criteria for the disorder have not been published. However, two recent groups of authors – Mendez and colleagues in

2002, and Tang-Wai and colleagues in 2004 – have taken it upon themselves to establish reliable criteria for diagnosing PCA. The proposed diagnostic criteria from both Mendez and Tang-Wai have received a lot of attention, and are now often cited as the criteria that patients must meet in order to be classified as having PCA (e.g. Josephs et al., 2006; Whitwell et al., 2007).

The most common symptoms of PCA include alexia, apperceptive visual agnosia, Balint's syndrome (now defined as: simultanagnosia, optic ataxia, and ocular apraxia), Gerstmann's syndrome (agraphia, acalculia, left-right confusion, and finger agnosia), ideomotor apraxia, anomia, and visual field deficits. Less common symptoms, such as spontaneous Parkinsonian symptoms and visual hallucinations, may develop later in the disorder and may be indicative of a specific underlying pathology or diagnosis, such as dementia with Lewy bodies (McMonagle et al., 2006; Tang-Wai et al., 2003; 2004).

As a syndrome, PCA is defined by a set of clinical symptoms, rather than an underlying pathology. Tang-Wai and colleagues (2004) suggest the following core features as the criteria for diagnosis with PCA: an insidious onset and gradual progression of visual symptoms without ocular disease, stroke, or tumor; the relative preservation of anterograde memory and insight early in the disorder; the absence of early parkinsonism and hallucinations; and the presence of any of the following: simultanagnosia with or without optic ataxia or ocular apraxia, constructional dyspraxia, visual field defect, environmental disorientation, and any elements of Gerstmann's syndrome. In addition, alexia, prosopagnosia, ideomotor or dressing apraxia, and presenile onset are suggested as supportive features. Mendez's diagnostic criteria are extensively the same as Tang-Wai's, the most significant difference being that Mendez and colleagues (2002) propose that all of the following: visual agnosia, dressing apraxia, environmental disorientation, and elements of Balint's syndrome *must* be present for diagnosis.

In practice, however, it seems that Mendez's more strict criteria are often not precisely followed in order for a diagnosis of PCA to be given. In fact, Tang-Wai argues that Mendez's criteria are too narrow, as they exclude the many individuals with PCA who do not present with dressing apraxia or environmental disorientation.

As previously mentioned, PCA results from progressive neurodegeneration that primarily targets occipital, posterior parietal, and posterior temporal cortices. However, since diagnosis with PCA is not defined by pathology, the course of the disorder, and indeed an individual's specific symptoms, may depend heavily on the responsible neuropathological entity. In as many as 75% of PCA cases, Alzheimer's pathology – a disruptive accumulation of neurofibrillary plaques and tangles – is the underlying cause (Renner et al., 2004). The remaining 25% of cases are made up of patients with corticobasal degeneration (CBD), dementia with Lewy bodies (DLB), and prion diseases such as Creutzfeldt-Jakob disease (McMonagle et al., 2006; Renner et al., 2004). Amongst those who share a common biological pathology, the pattern of cortical atrophy between patients does vary, so there is certainly a heterogeneity in the types and severity of symptoms exhibited. However, it is important to keep in mind that, regardless of the underlying pathology, studies have demonstrated a clear uniformity in the clinical profile of PCA (Tang-Wai & Mapstone, 2006 on McMonagle et al., 2006), justifying the argument for its recognition as a unique and definable syndrome.

PCA's relatively recent recognition combined with the scarcity of patients available for clinical testing means that there have been very few investigations into the deficits that accompany PCA. Some large-group studies have revealed common PCA symptoms and documented their prevalence (e.g. Mendez et al., 2002; Tang-Wai et al., 2004), but these reports do not give us detailed information regarding the manifestations of these deficits. Josephs and

colleagues (2006) recently probed a large population of PCA patients with regard to one particular symptom – visual hallucinations – and discovered that this symptom is specific to patients with CBD. Joseph et al.'s result demonstrates the merit and potential clinical application of further investigation into the symptoms, course, and etiology of PCA.

The proposed study seeks to investigate the prevalence and nature of visuomotor deficits in a small group of individuals with PCA. Specifically, these experiments aim to tease apart perceptual and visuomotor abilities, and quantify the loss of function to each of these faculties.

Reaching and Grasping

Interacting with the world around us seems like an easy, straightforward process – we see an object, we pick it up. Indeed, we effortlessly reach out and pick up dozens of objects every day. Nonetheless, this process is far from simple. The basic act of reaching out to grasp an object is a multi-stage operation that requires a vast number of rapid calculations and the cooperation of an extensive neural network. It is not enough to simply 'see' an object in order to grasp it; the object's precise size, shape, and location must be calculated. Our visual system cannot just tell us that an object is "about this big", "a little smaller than that other one", or "sort of round-shaped". Instead, our visual system needs to calculate *exactly* the dimensions of the object we wish to grasp in order for us to be as accurate as we are. Moreover, this very precise information about object properties must be coded with respect to the location of our hand and fingers, and the whole grasping process needs to be constantly updated and monitored as we carry out the movement. It is clear, then, that accurate prehension requires much more than just 'seeing'.

Two Stream Theory

At the heart of neurobehavioral doctrine is the idea that specific brain areas are tuned to perform specific functions. That is, different loci within the brain are responsible for different processes and, ultimately, different behaviours. A simple example of this is the motor cortex, in which neighbouring areas of cortex control the basic movements of different parts of the body. This functional localisation is also well established in the visual system; specific cortical locations, such as visual areas V4 and V5, are responsible for unique and specialised tasks — in this case colour and motion processing, respectively (Milner & Goodale, 2006). Additionally, cortical systems often rely on hierarchical structuring for the detailed and efficient processing of information, as well as for the generation of complex behaviors. This is particularly apparent in our perceptual system, where neurons respond to increasingly more complex stimuli as we work our way 'up' from primary visual (V1) to inferotemporal (IT) cortex (Milner & Goodale, 2006). These two phenomena – functional localisation and hierarchical organisation – form the basis of the two stream theory of visual processing.

The idea of multiple independent streams for visual processing is not a new one. Theories in the late 1960s proposed that visual information travelling to the midbrain may be responsible for different functions than visual information being fed to visual cortex. For example, Trevarthen (1968) suggested that midbrain systems guide whole-body movements, while the geniculostriate system guides more precise motor acts. Although Trevarthen's theory was soon superseded by others, it was one of a number of theories that were important in helping vision researchers conceptualise how visual information could be used for different purposes in different regions of the brain. Arguably, one of the most important theories to come from this idea is that of Ungerleider and Mishkin (1982), who proposed a functional distinction

between posterior parietal and inferior temporal cortices in terms of the processing of visual information that occurred there. This 'two cortical visual systems' theory identified a dorsal stream that was specialised for analysing the spatial relations between objects, and a ventral stream specialised for analysing an object's physical attributes. As such, a 'what' versus 'where' dissociation was proposed to define the processing that occurred in the ventral and dorsal streams, respectively. This theory was based on a wealth of data from both human neuropsychological and monkey neurophysiological studies. For example, monkeys with lesions to key areas in the ventral stream (IT cortex) have difficulties with pattern recognition (Ettlinger, 1959), while monkeys with dorsal stream lesions (posterior parietal cortex) show an inability to use objects as spatial landmarks (Pohl, 1973). Although Ungerleider and Mishkin's theory was elegant and tied together many neuropsychological observations, there was a growing amount of evidence that this theory failed to explain.

In the early 1990's a new theory challenged Ungerleider and Mishkin's 'what' versus 'where' idea. Based strongly on patient observations, it was proposed that the ventral and dorsal visual streams would better be classified as 'what' versus 'how', respectively (Goodale & Milner, 1992). Milner and Goodale rejected the idea that each stream was specialised for a different aspect of perceptual processing, and instead proposed that the ventral stream generates perceptual representations while the dorsal stream is responsible for visuomotor transformations. This theory argues that occipito-temporal cortex, which makes up the ventral stream, is responsible for the identification and recognition of objects. Specialised areas in this pathway, such as IT cortex, allow for the integration of visual information into a vivid and robust representation of an object. Furthermore, the ventral stream prepares these object 'percepts' for long-term storage and later retrieval from memory. This is made possible by the ventral stream's proximity to and inter-connectivity with medial-temporal cortex, which contains the

memory-specialised entorhinal cortex and hippocampus. Meanwhile, areas in the posterior parietal lobe, specialised for motion processing and sensory-motor integration, make up part of the dorsal stream, a pathway responsible for guiding our fast and accurate interactions with the objects around us.

Frames of Reference

Given the differences in how the two cortical streams use visual information, it should come as no surprise that each stream represents object information in a different way. As we have seen, the ventral stream is concerned with producing robust scene and object representations which allow us to store these percepts in memory, recognise the same objects from any vantage point, and judge the spatial arrangement of multiple items. To achieve these feats, visual information in the ventral stream is encoded in allocentric – object-based – coordinates, meaning that an object's properties, such as size, shape, and texture, are defined in relation to its environment and the objects around it. Meanwhile, the dorsal stream, concerned with representing objects in a way that facilitates our interaction with them, works off an egocentric – user-based – framework (Carey, Dijkerman, Murphy, Goodale, & Milner, 2006; Kosslyn et al., 1989). Thus, the dorsal stream relies on a coordinate system that bases its calculations on the position of the viewer – taking into consideration the orientation of the body, head, and eyes, as well as coding object properties with respect to the body part being used to manipulate that object (Milner & Goodale, 2008). For example, when reaching out to pick up a mug off the table, the dorsal stream will use visual information about the cup with respect to the hand in order to plan and guide an accurate grasping movement. Furthermore, there are multiple coding systems in the parietal lobe, each of which controls a different body part, or effector (Milner & Goodale, 2006).

Fitting with the idea that information in the ventral stream is accessible to our conscious, declarative system, while processing in the dorsal stream occurs more unconsciously, we have the ability to clearly articulate the type of coordinates used for coding objects in the ventral stream, but we are not privy to the same calculations made by the dorsal stream. For example, while we may be able to roughly describe the location of a coffee cup relative to other objects or to estimate its size and shape, we would struggle to define the exact angular position and distance to the cup with respect to our shoulder or hand – the type of information used by the dorsal stream to guide a precise grasp. In line with this dissociation is the fact that the ventral stream forms robust, long-lasting object representations that rely on categorical rather than coordinate information (Carey et al., 2006; Kosslyn, Chabris, Marsolek, & Koenig, 1992). Conversely, the dorsal stream's representation of an object is far more transient. Coding an object in a coordinate system based on the location of an effector is only useful if the position and orientation of the effector and the object are identical each time this precise interaction is required. Since this is a situation that does not occur very often, an egocentric object representation must be constantly updated to accommodate the fluid nature of our environment. As such, the dorsal stream's control of the visuomotor system relies on a constant influx of up-to-the-second visual information (Milner, Dijkerman, & Carey, 1999).

This difference in the properties of the coordinate systems in the dorsal and ventral streams is an important one in the context of the current study. First of all, there is evidence that egocentric coding is restricted to the dorsal stream (Committeri et al., 2004). Therefore, should damage to posterior parietal regions disturb the egocentric systems in the dorsal stream, there are no alternative egocentric maps in the brain for the visuomotor system to fall back on. Secondly, since the dorsal representation of an object is fleeting, the removal of 'on-line' visual information forces the visuomotor system to rely on more enduring, but less accurate, object

representations in the allocentric coordinate system of the ventral stream. In other words, introducing a delay into a visuomotor task forces a shift from dorsal to ventral control.

Ventral- and Dorsal-PCA

Given the variability in the location of atrophy exhibited in cases of PCA, it should not come as a surprise that attempts have been made to identify definable subtypes of the disorder. The most commonly suggested sub-classification of PCA is that of ventral and dorsal variants. Based on the two stream theory outlined above, this classification follows the idea that individual patients may have atrophy that primarily affects either the occipito-temporal or occipito-parietal visual processing streams. In such a situation, two distinct symptomologies could arise: patients with damage restricted to the dorsal pathway might exhibit Balint's syndrome, Gerstmann's syndrome, dressing apraxia, aphasia, and disorientation, while patients with damage to the ventral pathway might exhibit alexia without agraphia, visual object agnosia, and prosopagnosia (Tang-Wai et al., 2004). Rough examples of this dissociation have been documented in the literature. For example, Aharon-Peretz, Israel, Goldsher, and Peretz (1999) described four patients with probable PCA, two of whom initially presented with predominantly apraxic manifestations and two with predominantly visuospatial disturbances. Unfortunately, such a clear distinction is not always evident; many patients exhibit symptoms indicative of damage to both visual streams. Furthermore, a recent large-group study found that a pure ventral-stream syndrome seems to be quite rare (McMonagle et al., 2006). This observation is not hugely surprising considering the progressive nature of PCA, which often leads to very diffuse atrophy in the later stages of the disease. However, it does initially seem to pose a problem to the validity, or indeed usefulness, of the dorsal-ventral classification of PCA.

Why then, given the apparent weaknesses of a dorsal versus ventral classification, does this issue resurface so often in the literature (e.g. Galton, Patterson, Xuereb, & Hodges 2000; Nestor, Caine, Fryer, Clarke, & Hodges, 2003; Ross et al., 1996)? As we have already seen, PCA can be a very difficult disorder to diagnose, often requiring many different clinicians and many years of testing. This fact, coupled with the disease's progressive nature, means that PCA may indeed demonstrate a more localised onset – consistent with a theory of dissociable variants – which then becomes more obscured by diffuse atrophy at the time patients come to be tested. This hypothesis is strengthened by the previously presented examples of patients who do show a definite dissociation between dorsal and ventral symptoms. Further evidence in favour of the existence of localised variants of PCA comes from the observation of a few very rare cases in which atrophy is restricted to primary visual cortex (Galton et al., 2000; Levine, Lee, & Fisher, 1993). For these reasons, a ventral-dorsal sub-classification of PCA continues to be presented and discussed in the literature as a clinically useful diagnostic tool. Specifically, such a classification may aid in the early diagnosis of PCA, indicate the primary site of atrophy, and suggest the most appropriate course of therapy or disease management.

The Neural Control of Grasping

The seemingly very simple act of reaching out to pick up an object in front of you requires the participation of a surprising number of different brain regions. Primary visual areas in the occipital lobe, such as V1 and V2, extract basic form information regarding an object's shape, size, and orientation. These object features are sent for further processing to higher occipital and parietal areas that make up the dorsal stream. Here, vital visuomotor transformations are made to generate a motor plan based on the physical characteristics of the target. Motor plans from the parietal cortex ultimately make their way to premotor areas in the

frontal cortex for more accurate motor coordination and supervision of the movement, which is ultimately executed by control centers in primary motor cortex. This pathway is of great importance for the transformation of visual information into an accurate motor movement, and these brain areas are discussed in more detail below. However, other cortical and subcortical brain regions also play a role in grasping. For example, inputs from IT cortex provide important information regarding object meaning, while prefrontal and cingulate cortices make decisions regarding the appropriate manner in which to interact with an object (Castiello & Begliomini, 2008). As such, the intrinsic visual properties of an object do not solely dictate how a grasp will be executed. Rather, a multitude of other factors are taken into consideration, such as: the intended use of the object, how physically delicate the object is, how valuable the object is, or how potentially harmful the object may be. In addition, the cerebellum and basal ganglia are involved in the control and coordination of reaching and grasping movements. Studies using positron emission tomography (PET) have revealed cerebellar activity during grasping tasks (Grafton, Arbib, Fadiga, & Rizzolatti, 1996), and retrograde viral analyses have shown that inputs from both the cerebellum and basal ganglia into posterior parietal and premotor areas are involved in grasping (Clower, Dum & Strick, 2005; Hoover & Strick, 1999). Furthermore, patients with cerebellar and basal ganglia disorders "exhibit a spectrum of kinematic impairments in the learning, planning, and executions of prehensile movements" (Castiello & Begliomini, 2008).

Parietal lobe. It has long been known that the parietal lobe plays a key role in the visuomotor transformations required for proper reaching and grasping. Over 30 years ago it was noted that monkeys with lesions to the inferior parietal lobule demonstrate inaccurate reaching, failures to properly shape the hand, and awkward grasping (Faugier-Grimaud, Frenois & Stein, 1978; Haaxma & Kuypers, 1975). Since then, more sophisticated stimulation, recording, and imaging techniques have revealed a multitude of discrete, but highly interconnected, modules

throughout the parietal cortex that participate in prehensile control. Each of these areas plays a specific role in the many different processes required for a reach-to-grasp action, such as: localising an object in extra-retinal coordinates, directing spatial attention, generating motor programs, monitoring hand movements, and providing on-line corrective feedback. I will discuss a number of these important regions, including the parietal-occipital area (PO), the medial intraparietal area (MIP), the anterior intraparietal area (AIP), and the medial dorsal parietal area (MDP).

AIP. Area AIP is one of the most-studied parietal regions involved in prehension. Located at the rostral end of the posterior bank of the intraparietal sulcus (IPS) in the monkey brain, AIP has been isolated and identified as being highly involved in grasping. This small region contains neurons that not only selectively fire during grasping tasks, but also show a preference for the type of grip being used and certain features of the object being grasped. Sakata and colleagues found that neurons in AIP showed selectivity for grasps made to specific objects; when presented with a broad variety of object shapes, AIP neurons only fired when monkeys grasped one or two of them (Sakata, Taira, Murata, & Mine, 1995). In addition to shape-preference, some of these same neurons were selective for an object's size and orientation. Importantly, this activity was not influenced by the object's position in space, showing that AIP is concerned with the specific hand and finger movements required to grasp the target rather than the proximal arm movements needed to move the hand into position. Sakata categorised AIP neurons into three distinct groups based on their responses to grasping motions made either in the dark or under visual guidance: 'motor dominant' neurons fire during grasping in the light and in the dark, 'motor or visual' neurons fire under both grasping conditions but are less active in the dark, and 'visual dominant' neurons are active exclusively in the light. 'Visual dominant' neurons can be further subdivided into 'object' type neurons, which fire simply at the sight of a

specific object, and 'non-object' type neurons, which respond to a moving hand or the interaction of a hand with an object. In addition to encoding grip type and object properties, there is also evidence that AIP is modulated by contextual information regarding upcoming grasps. Baumann and colleagues recently demonstrated that as many as 25% of cells in macaque AIP respond simply to an instruction on which grip type should be used for a future grasp, without the target object even being seen (Baumann, Fluet & Scherberger, 2009). These results implicate area AIP in the context-dependent enhancement of motor-relevant object features – a vital step in the visuomotor transformations required for accurate grasping.

Importantly, there is mounting evidence for a human homologue of monkey area AIP. First, grasping studies using PET and fMRI have revealed a consistent activation of human AIP (hAIP; e.g. Biagi, Cioni, Fogassi, Guzzetta, & Tosetti, 2010; Grafton et al., 1996), and patients with lesions to hAIP show deficits in grasping but not in reaching (Binkofski et al., 1998). Second, we see bilateral activation of hAIP in response to grasping movements made with either hand, but the activation is greater in the hemisphere contralateral to the hand performing the grasp (Culham, Cavina-Pratesi, & Singhal, 2006). Third, inactivation of hAIP using transcranial magnetic stimulation (TMS) produces a delay in participants' abilities to adapt their grasp to a sudden perturbation of object orientation (Tunik, Frey, & Grafton, 2005). Tunik and colleagues saw a dissociation between the reach-phase and the grasp-phase of the movement; the time taken to grasp the object was affected by the TMS, while the time taken to reach the object remained unaffected. Finally, a recent study has shown that, as with monkeys, hAIP activity seems to be tuned to the type of grasp being used, with precision grasps being over-represented compared to whole-hand grips (Begliomini, Wall, Smith, & Castiello, 2007).

*PO–V6/V6a***.** Area PO has long been implicated in visuospatial functioning, especially with respect to peripheral stimuli, and, given its many connections with higher parietal regions known to be involved in controlling eye- and hand-movements, has since been the focus of many investigations into the control of prehension. PO is at roughly the same level in the hierarchy of visual cortical areas as V4 and V5 (Colby, Gattass, Olson, & Gross, 1988), and is therefore not as specialised in its control of grasping as areas such as AIP. In fact, area PO is now known to be made up of two cytoarchitectonically and functionally distinct areas: V6 and V6a (Luppino, Hamed, Gamberini, Matelli, & Galletti, 2005). These two areas are very strongly interconnected, and both project to the dorsal premotor area (PMd), the ventral premotor area (PMv), and the supplementary motor cortex (SMA) in the frontal lobe (Caminiti et al., 1999). However, V6a is considered to be higher in the visual hierarchy than V6, as V6 is more strongly connected with lower visual areas such as V2, V3, and V3a, while V6a receives ascending inputs from V5 but not from V2 and only weakly from V3 and V3a (Shipp, Blanton, & Zeki, 1998). V6 and V6a both have strong connections with 'higher' parietal areas such as MIP, MDP (also defined as PEc or 7m), LIP, and VIP, but their projections to PMd suggest that V6 and V6a are used for skeletomotor rather than oculomotor output (Shipp et al., 1998). Importantly, 'reaching cells' in area V6a have been discovered that code the direction of arm movements (Marzocchi, Breveglieri, Galletti, & Fattori, 2008). Some of these reaching cells have been shown to code activity retinocentrically while others code activity spatially, but the majority of these neurons use a coordinate system that incorporates both of these reference frames (Marzocchi et al., 2008). These properties suggest that V6a may play a key role in translating visual object information from an eye-centered frame of reference into an arm-centered frame of reference – another important step in the visuomotor transformations that underlie accurate object interactions.

In recent years, area V6a has come to the focus of many grasping researchers due the mounting evidence in favour of the human superior parieto-occipital sulcus (SPOC) being its functional human homologue (Culham, Cavina-Pratesi, & Singhal, 2006; Gallivan, Cavina-Pratesi, & Culham, 2009; Pitzalis et al., 2006). This association started to be made following lesion studies to area V6a in monkeys, which produced similar deficits to those seen in human optic ataxia patients. Battaglini and colleagues (2002) found that animals with V6a lesions produced abnormally scaled grip apertures and were unable to properly rotate their hands to match the orientation of a food slot. This set of deficits corresponds nicely with observations that optic ataxia patients show abnormalities in reaching movements, adjusting their hand orientation, and properly shaping their grip during prehension (Jakobson, Archibald, Carey & Goodale, 1991; Jeannerod, 1986; Perenin & Vighetto, 1988). Galletti and colleagues suggest that area V6a is part of a 'fast' visual system, responsible for unconscious, online corrections of hand movements during target-interactions (Galletti, Kutz, Gamberini, Breveglieri, & Fattori, 2003). They argue that neurons in area V6a respond with a very short latency to changes in the location, orientation, size and direction of movement of graspable objects, and quickly communicate this information with premotor cortex through its direct connections with PMd. As such, V6a, and its putative human equivalent, SPOC, may play a vital role in monitoring and correcting any mismatch between the intended movement of the hand and its actual trajectory.

PPC–PRR. Closely related to area V6a is the so-called parietal reach region (PRR). Sometimes used as a more generic term for the area of posterior parietal cortex (PPC) showing reach related activity, the PRR has been more recently defined in monkeys as a specific area on the medial bank of the IPS containing area MIP and potentially overlapping with V6a (Cohen, Batista & Andersen, 2002). Neurons in the PRR are highly active during the planning stages of reaches, both to visible and remembered targets. Many of these neurons are highly specific to

reaching movements, as one third of PRR cells respond to an instruction to plan a reach but not to an instruction to prepare a saccade (Calton, Dickinson & Snyder, 2002). Calton and colleagues also found that two thirds of cells in the PRR become activated in response to information regarding target location without any instruction as to the type of movement to be made. Additionally, during memory-guided reaches to multiple objects, activity in the PRR is selective for the reach about to be performed rather than for the targets of subsequent reaches, implicating this area in the target-specification of an *impending* reach (Batista & Andersen, 2001). Together, these observations provide evidence that the PRR in monkeys plays an important role in specifying potential motor responses to particular targets (Calton et al., 2002). Similar activity has been seen in a potentially homologous region of human PPC which responds preferentially during the delay period in memory-guided pointing tasks but not memory-guided saccadic tasks to the same location (Connoly, Andreson & Goodale, 2003). The authors suggest that this 'human PRR', located within the precuneus, encodes the intention to make a specific reaching movement to a specific location.

The PPC appears to have a very similar functional organisation in both monkeys and humans. In both species, the lateral intraparietal (LIP) sulcus is far more active during eye movement planning while the medial intraparietal (MIP) sulcus responds preferentially to the planning of reaches (Andersen & Buneo, 2002). These two regions, while mediating different tasks, share many properties, and communicate with each other to streamline motor actions. For example, both LIP and MIP encode their targets and their intended actions in a similar fashion – using a continuum between eye- and head-centered reference frames (Mullette-Gillman, Cohen, & Groh, 2005). Additionally, 'reaching cells' in MIP update their target-related activity if a saccade occurs during a delayed-reaching experiment (Batista & Andersen, 2001). Within monkey MIP, cells in different layers have been found to have different functions. Some

cells are highly specific, responding to passive manipulation of the contralateral arm, reaching movements made in the dark, or to purely visual stimuli in the contralateral periphery. Other cells are more general, responding to both visual stimuli and passive arm manipulation (Colby & Duhamel, 1996). More recently, fMRI studies have provided evidence for many of these functional properties, such as regional activity during contralateral pointing movements and eye-position modulation, also being present in humans (DeSouza et al. 2000; Medendorp, Goltz, Vilis, & Crawford, 2003). As might be expected, MIP maintains many reciprocal connections with the functionally similar region V6a (Shipp et al., 1998), and also shares many of the same projections – communicating with MDP (Pandya & Seltzer, 1986), V6 (Shipp et al., 1998), VIP (Lewis & Van Essen, 2000), and PMd (Caminiti et al., 1999). Together, these observations reveal the presence of a human PRR within the PPC that encodes movement goals in visual coordinates, and communicates these goals with other parietal and frontal regions involved in reaching and grasping movements (Fernandez-Ruiz, Goltz, DeSouza, Vilis, & Crawford, 2007).

Additional parietal areas. While the previously discussed regions are those that are the most directly involved in planning grasps to visual targets, a few other parietal regions play supportive roles in this process. As mentioned above, the precuneus has been identified as the site of a putative human homologue of the monkey PRR. However, the precuneus has also been implicated in controlling important processes that aid in the planning and preparation of individual movements. For example, the precuneus directs and shifts attention in space when imagining or preparing for movements (Cavanna & Trimble, 2006), and aids premotor areas in visuospatial mental operations (Oshio et al., 2010). Area MDP, which maintains connections with a multitude of areas involved in visuomotor operations – V6a, the frontal eye field (FEF), SMA, and PMd – plays a role in the coordination of head angle and hand position (Ferraina et al., 1997), and is thought to be an intermediate link in the cortical network underlying visually

guided reaching (Caminiti, Ferraina & Johnson, 1996). Finally, areas 7a and 7b, located in the medial and lateral portions of the IPL, respectively, play important roles in spatial perception and motor planning. Specifically, 7a is thought to play a crucial role in spatial perception, and its properties are highly modulated by shifts in attention (Quraishi, Heider, & Siegel, 2007). Cells in this area respond to both visual and motor stimuli, and they maintain connections with a huge variety of higher-level cortical areas in almost all regions of the brain (Andersen, Asanuma, Essick, & Siegel, 1990). This connectivity is unique amongst visual areas in the IPL, as 7a is the only area that connects with higher brain centers in the cingulate, parahippocampal, and superior temporal sulci. Importantly, this last region contains IT cortex, thus providing a direct connection between the areas thought to be most crucial for object and spatial perception (Andersen et al., 1990).

Frontal lobe. In the frontal cortex, a number of different premotor and supplementary motor areas have been identified that play a key role in reaching and grasping. One region that maintains a great number of reciprocal connections with area AIP is monkey area F5, located in the ventral premotor area (PMv; Taira, Mine, Georgopoulos, Murata, & Sakata, 1990). Activity in F5 is correlated with specific goal-related distal movements (Kurata & Tanji, 1986; Rizzolatti et al., 1988), with most neurons in this area controlling object-related actions, such as grasping, holding, tearing, and manipulating (Jeannerod et al., 1995). These grasping neurons not only show a specificity for the type of prehension that is performed – the majority favouring a precision grip – but also for different finger configurations within a certain type of grip, and for the size of the target stimulus (Rizzolatti et al., 1988). Unlike AIP neurons, which fire for the duration of an action, F5 neurons fire selectively at particular segments of an action (Jeannerod, Arbib, Rizzolatti, & Sakata, 1995). Because of this, it is said that F5 contains motor schemas that form a basic ‘vocabulary’ of dexterous movements. Finally, F5 also contains a minority of visually

responsive neurons that either respond to the presentation of a graspable object, or to movements performed by another individual that are similar to those encoded by that neuron (Jeannerod et al., 1995). This latter group, known as mirror neurons, plays an important role in motor skill development and vicarious learning. Imaging studies have so far failed to find activity related to reach-to-grasp movements in human PMv (Castiello & Begliomini, 2008). Given the similarities between monkey and human cortex, however, it seems reasonable that a functionally homologous area to F5 must exist in a similar location in the human brain. More targeted imaging studies may reveal a human homologue in the coming years.

A number of other frontal areas have also been found to play important roles in reaching and grasping. One of the more important of these is area F2, also known as the dorsal premotor cortex (PMd). Monkey studies have shown that neurons in F2 show activity related to specific parameters of reaching and grasping movements. For example, some F2 neurons are selective for the direction and amplitude of movements made by the forelimb (Caminiti, Johnson, Galli, Ferraina, & Burnod, 1991), while others are selective for the type of prehension required to grasp an object (Raos, Umilta, Gallese, & Fogassi, 2004). F2 is similar to F5 in that it codes grasping actions as a whole, rather than individual finger movements. In fact, neurons in F2 show very similar response properties to those in F5 (Raos et al., 2004). Roas and colleagues have therefore posited that F2 may be responsible for monitoring ongoing grasps and updating hand movements by comparing the current grip-state with the motor representation selected by F5. Importantly, recent imaging studies with humans have found evidence for bilateral PMd activity during grasping tasks, where PMd seems to play a crucial role in the monitoring of finger positions during grasp planning and execution (Begliomini et al., 2007).

Other frontal areas, such as F4 and F6, also participate in the planning and control of grasping movements. F4 has been found to be involved in space perception, and plays a key role in the transformation of peripersonal coordinates into head and arm movements (Rizzolatti, Fogassi & Gallese, 2002). Additionally, most F4 neurons have receptive fields that are coded in reference to a specific body part, independent of eye position (Fogassi et al., 1996). In this way, F4 may work in harmony with the dorsal stream in the production of actions based on an egocentric frame of reference. F6, which makes up part of the more broadly defined supplementary motor area (SMA), makes connections with more executive areas of the frontal cortex, such as the dorsolateral prefrontal cortex (DLPFC), as well as limbic areas. Through these connections, F6 is thought play a role in the selection and preparation of movements, as well as the control of action timing with regards to external factors and internal motivation (Luppino & Rizzolatti, 2000). In terms of grasping, F6 neurons show preparatory activity in the time leading up to a grasp, and their responses are modulated by the movement of a graspable object into or out of an animal's peripersonal space.

Patients

For the last two years, we have been working with four patients in Winnipeg who have been identified as exhibiting PCA-like symptoms by neurologist Dr. Paul Shelton. All four individuals are aware of their deficits and have expressed a keen interest in helping to advance the clinical understanding of their disorder. To this end, they have agreed to participate in various psychometric and neuroimaging studies run by members of the University of Manitoba's *Neuropsychology of Vision: Perception and Action Lab*.

Patient RB

As previously introduced, RB is a 75 year-old female who first demonstrated symptoms of PCA three to four years ago. These difficulties initially manifested as trouble recognising recent photographs of family members and friends following her 50th wedding anniversary. Around the same time, her husband noticed that she had great difficulty making out the number of dots on dominos tiles, even after she viewed the tiles under multiple light sources. Since these initial problems, she has developed generalised colour disturbances, severe prosopagnosia, visual object agnosia, simultanagnosia, and apperceptive visual agnosia. These deficits were apparent from her initial visit to our lab, and a subsequent visit to a behavioural neurologist, Dr Paul Shelton. RB scored 1/50 on a famous faces task and 5/15 on the Boston naming task for basic objects. She was also severely impaired on the Benton Visual Form Discrimination Task (VFDT), scoring 20/32 (Campo & Morales, 2003). RB had great difficulty accurately copying simple line drawings: her lines were disproportionate in size and not properly oriented, and she had trouble putting individual aspects of a drawing together to complete an object (Dr P. Shelton, personal communication, September, 2008). Although RB performed fairly well on a basic object counting task, scoring 13/14, simultanagnosia was apparent from her performance on object identification tasks where she seemed to "focus her attention on one aspect or one detail of the visual form and then be unable to use any additional features to form a whole concept of what she is looking at" (Dr P. Shelton, personal communication, September, 2008). It is also interesting to note that although RB can correctly name colours, she was unable to trace a colour pattern on an Ishihara colour plate – perhaps a product of her simultanagnosia. At the time of her first visit, RB was still an avid reader, getting through two newspapers a day. However, her husband notes that she has trouble "getting the words out" from time-to-time, and Dr. Shelton reports that RB has some trouble reading – especially if the script is written in

cursive handwriting or a flowing script – and that she sometimes engages in letter-by-letter reading. RB's husband mentioned that his wife seems a little more forgetful these days – forgetting the meaning of a flashing red traffic signal, for example. However, neither RB nor her husband report her having any major memory issues, and her neurologist noted the absence of any memory deficits on her first visit. Although she suffers from cataracts and mild macular degeneration, RB has no problem making out letters, and she performs well on tests of visual acuity, scoring 20/25 on a visual acuity chart.

Patient MTB

MTB is a 65 year-old female who started to develop symptoms of PCA almost eight years ago. MTB first visited us in early 2009 following a referral from her neurologist, Dr. Shelton. In 2002, MTB started to develop problems with her vision and motor coordination. Since then, her visual and motor problems have progressed to the point where she no longer reads or operates a vehicle. She has difficulty discriminating right from left, and has developed an unsteady gait. Despite the fact that she has stopped reading at home, MTB was able to correctly read out-loud 10/10 sentences with a restricted set of stimuli. However, the process of reading is an arduous one, and she claims that the letters "jump around" on her. This same problem impairs her performance on basic copying tasks, as she complains that the object she is trying to draw is "dancing" on the page. MTB has not complained of memory issues or problems with face recognition, and she correctly identified 15/15 objects on the Boston naming task. However, on a preliminary famous faces task, MTB successfully identified only 32/50 (64%) people, as opposed to her husband who identified 46/50 (92%) of the same faces. While MTB's poor performance could be a result of a number of factors – less exposure to these famous people, or a poorer memory for faces – it could also indicate a subtle deficit in face perception.

As would be predicted by her apparent simultanagnosia, MTB performed poorly on a basic object-counting task, scoring only 7/14 (50%). Finally, and unlike RB, MTB has reported having trouble accurately interacting with objects when trying to pick them up.

Patient SS

SS is a 64 year-old male who first came to our lab in January of 2010. He and his family first noticed problems in August of 2007, when he seemed to have difficulty finding his way through the city to meet an old colleague. Since then, SS – who previously had a very good sense of direction – has gradually and progressively developed pronounced deficits in route finding and spatial orientation. For example, at a restaurant, SS found himself unable to find his way back to his table after visiting the washroom, and, while on a cruise ship last year, he repeatedly got lost on deck. These problems have recently progressed to the point where he has trouble navigating through his own house – often unable to find his way to the basement. As a result, like so many of our PCA patients, SS has now completely given up driving, and won't leave the house alone. Additional perceptual deficits have plagued SS, such as difficulty finding objects in front of him that, according to his family, seem to be in plain view. Although he has macular degeneration, ophthalmologists have failed to find a purely visual cause for his problems. In addition to his perceptual difficulties, SS can no longer perform simple calculations, and, despite being a retired accountant, he cannot manage his family's finances.

SS visited Dr. Shelton in October of 2009, and underwent a battery of standardised tests. Dr Shelton found that SS retained insight into his disorder, but unlike our other patients, he sometimes required some prompting to describe his problems. His conversational speech was good, but he demonstrated minor word finding and semantic paraphasic errors – sometimes replacing words with similar, but incorrect words, such as 'dog' with 'cat'. In reading

and writing tasks, SS read correctly only 2/10 sentences, made spelling errors in his writing, and both his reading and writing were telegraphic – often missing important words. On formal testing, SS showed difficulty with executive functioning – performing slowly at number cancellation, for example – but was not impaired on tests of executive function that were free of spatial elements, such as verbal fluency. As such, SS proved to be "severely impaired in tasks depending upon visual scanning and motor response [involving] spatial location" (Dr. P. Shelton, personal communication, October 22, 2009). For example, he performed very poorly on Bell's object cancellation task, correctly finding only 10/34 targets – missing all of those located in the lower visual hemispace. Similarly, he was severely impaired on the Rey-Osterreith Complex Figure (ROCF) copying task, scoring 5/36, and the clock drawing task, scoring 5/15. SS also demonstrated some object agnosia, scoring 19/30 on both object naming and object recognition tasks. His face perception was similarly affected, as he scored 8/20 and 14/20 on tests of face naming and face recognition, respectively. Dr. Shelton suggested that these deficits may be secondary to a spatial perceptual disorder, such as simultanagnosia, given that SS demonstrated great difficulty relating parts of an object to a whole, and often focused his attention on the local features of a display. For example, when asked to identify a ball decorated with stripes and stars, he saw only stars, and when asked to copy an image he couldn't identify, he drew specific details of the object scattered around the page.

In addition to perceptual deficits, Dr. Shelton also reported evidence of optic ataxia, as SS demonstrated misreaching and inaccuracy when shaking hands or pointing to a target. He showed some evidence of slowed limb movement – bradykinesia – and cogwheel rigidity in his arms. SS was moderately impaired at copying novel hand movements and failed on motor sequencing tasks – indicative of ideomotor apraxia. These types of problems have also been noticed by his family, as his daughter mentions that he struggles with "sequencing tasks both in

terms of being able to figure out himself in what order to do activities […] and when you tell him to do something that involves multiple steps" (personal communication, March 13, 2009). Finally, Dr. Shelton reports mildly impaired memory, but states that this problem "appears to be primarily a retrieval deficit as opposed to involvement of the medial temporal memory system" (personal communication, October 22, 2009). SS scored 20/30 on an MMSE.

Patient AP

AP is a 77 year-old, left-handed female who first visited us in December of 2009. A retired journalist, AP suffers from a variety of symptoms consistent with PCA. As with many of our patients, her first and major complaint is difficulty reading. She reports that the words "jump" on her, and she struggles to find her place in a line of text. Between her first examination in March of 2009 and her second eight months later, Dr. Shelton noted a worsening of AP's visual impairments. At the time of her second appointment she had stopped reading because it had become too slow and effortful a task – depriving her of her main source of enjoyment. This difficulty seems to be attributable to "visual spatial and spatial attentional deficits" (Dr. P. Shelton, personal communication, November 12, 2009) rather than a pure alexia, as isolating letters or words enables AP to read quite fluently. Further testing by Dr. Shelton revealed misreaching consistent with optic ataxia, slowed limb movements, and right-side tactile extinction. Additionally, AP showed bilateral hemispatial neglect that was more pronounced on the right. Consistent with this unilateral neglect, AP performed poorly on line bisection tasks – misbisecting lines to the left – and consistently pointed to the right of a target, albeit to a small degree. As is common in PCA, AP reported dressing apraxia – needing help to get her clothes turned around the right way before she could get them on. She also showed a mild increase in muscle tone and demonstrated dysarthria – sometimes struggling to generate

fluent speech. Finally, AP demonstrated deficits indicative of simultanagnosia, and was severely impaired in judging line orientation – scoring only 1/12 on a line orientation task. Unlike many of our previous patients, however, AP placed in the normal range for object and face perception tasks – scoring 26/30 on object recognition, 8/10 on face naming, and 9/10 on face recognition tasks (Dr P. Shelton, personal communication, November 12, 2009).

Experiments

The primary purpose of the current investigation was two-fold: to provide a precise and targeted exploration of the visuomotor deficits associated with PCA with regards to prehensile actions; and to determine the differential impact of PCA on the two streams of visual processing in a small group of patients. To achieve these goals, three independent studies were performed, each of which sought to examine a unique aspect of the prehensile process and provide conditions that taxed a specific facet of the neural underpinnings of reaching and grasping movements. Additionally, the first two tasks were designed to allow for a direct comparison of functioning between the dorsal and ventral visual streams. This comparison was made possible by varying either the task demands or the task conditions while maintaining stimulus consistency.

Patients and controls were tested both at the University of Manitoba's *Neuropsychology of Vision: Perception and Action Lab* and in their homes. Testing sought to probe the quality of participants' visuomotor abilities, specifically targeting their ability to execute accurate grasps to real, three-dimensional objects. All statistical tests adopted a type-1 error rate of $\alpha=0.05$, with calculated p-values being considered significant if they fell below this value. Healthy age-matched controls were recruited to provide comparison data. An effort was made to have a control group for each test that included two age-matched controls for each patient. Not all

control participants were willing to participate in every study, so 11 controls had to be tested in order to provide an adequate group size for each experiment.

Basic Testing

Methods. All participants underwent an initial battery of basic visual, motor, and cognitive tests to uncover any visuomotor or cognitive deficits that may have influenced testing performance. A basic Edinburg handedness inventory (Oldfield, 1971) was run to determine hand-dominance. This inventory was used to ensure that participants' stated hand-preferences aligned with their natural hand-dominance. It also provided an opportunity to assess participants' abilities to follow basic motor commands.

Vision was tested using the Snellen Chart for visual acuity, the Pelli-Robson Contrast Sensitivity Chart (Clement Clarke International, Harlow, UK), and the Randot SO-002 test of stereo acuity (Stereo Optical, Chicago, IL). Additionally, visual field tests were obtained from participants' optometrists or ophthalmologists where available. These visual tests were chosen to help determine whether or not participants had basic visual difficulties that could hinder their performance on more advanced tests of visuomotor functioning, or that may explain any perceptual or visuomotor deficits. Unfortunately, since both the Snellen Chart and Pelli-Robson Contrast Sensitivity Chart depend on letter recognition, it proved impossible to ensure that patients' performances on these tasks were not being negatively influenced by difficulties in letter identification. As a result, contrast sensitivity scores were not obtained from the patient group, and optometrist reports were referenced to gather reliable visual acuity information.

Visual perception was evaluated using a number of established tests: Benton face task (Oxford University Press, New York, NY), Benton Visual Form Discrimination task (VFDT; Oxford University Press, New York, NY), Benton Line Orientation task (Oxford University Press, New

York, NY), and the Boston naming task (Pro-ed, Austin, TX). Custom made tasks for 'object counting' and 'object naming' were also run. Together, these tasks provided a reasonable account of participants' perceptual abilities – from basic shape discrimination to more complex face perception.

Two tests of reaction time were administered as measures of psychomotor processing speed (Salthouse, 2000): a repetitive finger tapping task (Veeder-Root, Hartford, CT) and a simple reaction time task. The reaction time task was custom made and programmed in E-Prime software (Psychology Software Tools, Pittsburgh, PA). It required patients to hit a single key as fast as possible in response to the appearance of a visual stimulus – a large red dot – on a computer screen. Reaction times have been suggested as a useful measure of general neural integrity (MacDonald et al., 2008), and extensive norms exist for this simple task (Der and Deary, 2006).

Finally, basic cognitive abilities were assessed using the Mini Mental State Examination (MMSE; M. Folstein, S. Folstein & McHugh, 1975) and the Dementia Rating Scale (DRS-2; Psychological Assessment Resources, Lutz, FL). The DRS-2 consists of five subscales: Attention (ATT), Initiation/Perseveration (I/P), Construction (CONST), Conceptualisation (CONCEPT), and Memory (MEM). Steven Mattis (2004), co-developer of the DRS-2, describes these subscales as follows:

> The ATT subscale measures working memory (i.e. forward and backward digit span) and the ability to attend to and execute verbal and visual commands of varied complexity. […] The I/P subscale consists of items that assess verbal generative fluency, auditory articulation of vowel and consonant patterns, double alternating motor movements, and simple graphomotor skills. […] The CONST subscale measures the ability to copy

> simple visual designs and sign [their] own name. […] The CONCEPT subscale assesses abstract concept formation skills and the ability to identify similarities and differences among sets of objects presented both visually and verbally. […] The MEM subscale measures orientation (to time, day, date, and situation), recall of verbal information after a brief delay, and verbal and visual forced-choice recognition memory.

In addition to testing for signs of dementia, scores from the MMSE and DRS-2 allowed us to better compare our participants to other neurological patients and controls. For example, the MMSE is a very commonly administered cognitive assessment used by investigators working with PCA patients (e.g. McMonagle et al., 2006; Charles & Hillis, 2005; Schmidtke et al., 2005; Nestor et al., 2003; Zakzanis & Boulos, 2001). Furthermore, even though scores on the MMSE vary by age and education, extensive norms exist in the literature, making the MMSE useful for patient comparisons with matching population reference groups (Crum, Anthony, Bassett, & Folstein, 1993).

Additional information that could influence performance was collected from participants in the process of administering other tests or filling out other forms. For example, years of formal education was recorded as part of the DRS-2, and a list of current medications was provided as part of an MRI pre-screening form (administered outside of the current study).

Results.

Controls. All controls were shown to be right hand dominant by the Edinburgh Handedness Inventory. None showed any deficits in basic visual acuity or contrast sensitivity. Visual field tests were available for two controls. One, GI, showed normal vision with both eyes, while the second, II, showed a generalised loss of sensitivity with his left eye – though no obvious deficit, and some loss of sensitivity in his superior field of vision with his right eye. One

control, TS, was stereoimpaired, failing to identify stereograms below 400 seconds of arc (arcsec) on the Randot SO-002 graded circles test. All others were able to identify stereograms below 100 arcsec, and would be considered stereonormal (Zaroff, Knutelska, & Frumkes, 2003).

Control participants all scored either 29 or 30 out of a possible 30 points on the MMSE. Total Scores on the DRS-2 ranged from 134 to 144 out of a possible 144 points, which correspond to Age-Corrected MOANS Scaled Scores of between 9 and 16 for the individual control participants, covering a range of "below average" to "average" for their respective age-groups. No control subject fell outside of the "normal" range for either test.

The control group showed an average median reaction time of 294ms, which produces a 95% confidence interval (C.I.) of 200ms to 388ms. This reaction time is very close to the normal range for people of that age group (Der & Deary, 2006). On the repetitive finger tapping task, controls produced an average of 35.2 taps/10s with their right hands, giving a 95% C.I. of 16.6 taps/10s to 53.8 taps/10s, and 31.0 taps/10s with their left hands, giving a 95% C.I. of 16.3 taps/10s to 45.6 taps/10s.

One control scored 13 out of 14 on the object counting task, while the others all produced perfect results. Two controls scored 17 out of 18 on the object naming task – likely due to English being their second language, while the others all scored the full 18. The control group scored an average of 14 out of 15 on the Boston Naming task (range: 11-15), an average of 29 out of 32 on the Benton VFDT (range: 25-32), an average of 24 out of 30 on the Benton Line Orientation task (range: 18-30), and an average of 48 out of 54 on the Benton Face Recognition task (range: 41-54).

RB. RB was shown to be right hand dominant by the Edinburgh Handedness Inventory, and was able to pantomime general tool use – such as cutting bread with a knife or hammering

a nail. RB was stereonormal, identifying stereograms at 70 arcsec. RB's vision is corrected-to-normal and neurologists report that her visual perception problems are not due to diplopia (double vision), deficits in visual acuity, or visual field impairments (Dr. S. Black, personal communication, May, 2010).

RB scored 26 out of a possible 30 points on the MMSE, which falls within the normal range for healthy populations in her age-group (Crum et al., 1993). She obtained a DRS-2 Total Score of 126 out of a possible 144 points (see Table 1.a), which corresponds to an Age-Corrected MOANS Scaled Score of 6 (6-10 percentile range) and indicates a mildly impaired level of performance. Based on RB's 15 years of formal education, this Total Score corresponds to an Age- and Education-corrected MOANS Scaled Score of 5 (3-5 percentile range) and indicates a moderately impaired level of performance. Breaking her results down by subtest, we see that RB was below average, but intact, for I/P and MEM. The I/P subtest showed that she had no problem quickly naming a list of different items that can be bought at the supermarket, and she could easily produce repetitive alternating hand movements. She failed to accurately replicate a drawing of alternating square-triangle "ramparts", but was able to reproduce an alternating "XO" pattern. RB showed perfect orientation responses (day, date, location, Prime Minister, etc.) on the MEM subtest, and was perfectly able to recognise which item she had just been told on a forced-choice task. RB's scores on the CONCEPT and ATT subtests ranked as mildly impaired. When shown a set of three simple designs on the CONCEPT subtest, she was very good at identifying which two were the same or most alike, but when she was shown these same designs again and asked to identify which of the three was different or didn't belong, she failed on half the items. RB had no problem repeating strings of numbers both forwards and backwards as part of the ATT subtest, but performed very poorly in a visual search test to find all

Table 1.a. *DRS-2 Summary Table for patient RB*

Scale/Subscale	Raw Score	Age-Corrected MOANS Scaled Score (AMSS)	Age- and Education-Corrected MOANS Scaled Score (AEMSS)	Percentile Range
Attention	31	6		6-10
Initiation/Perseveration	36	10		41-59
Construction	3	3		1
Conceptualisation	33	8		19-28
Memory	23	10		41-59
DRS-2 Total Score	126	6	5	3-5

Table 1.b. *DRS-2 Summary Table for patient MTB*

Scale/Subscale	Raw Score	Age-Corrected MOANS Scaled Score (AMSS)	Age- and Education-Corrected MOANS Scaled Score (AEMSS)	Percentile Range
Attention	33	7		11-18
Initiation/Perseveration	33	6		6-10
Construction	1	2		<1
Conceptualisation	38	11		60-71
Memory	20	5		3-5
DRS-2 Total Score	125	5	4	2

the letter 'A's in a field of letters, especially when the orientation and size of the letters was not constant. However, she correctly matched 3 of 4 visual designs, and accurately identified previously presented visual designs on 3 out of 4 trials on a visual memory test. Finally, RB was severely impaired on the CONST subtest, being unable to accurately reproduce unequally spaced vertical lines, a diamond in a box, or a side-by-side square and diamond. It wasn't until she was presented the square and diamond pictures individually that she was able to replicate the shapes.

RB's median reaction time of 560ms was significantly slower than the control group ($p<0.05$). On the repetitive finger tapping exercise, RB produced 19 taps/10s with her right hand and 18.5 taps/10s with her left hand. Even though these rates fall within the 95% confidence interval of control data for both hands, her ability to produce rapid, repetitive motor movements was clearly towards the lower end of the normal range.

On a basic object counting task, RB scored 12 out of a possible 14. She correctly identified only 5 of 18 objects on a basic object naming task, and 1 out of 15 on the Boston Naming task. She found the Benton Line Orientation extremely difficult, scoring 0 on the 5 trials attempted. RB also demonstrated five peripheral, four major rotation, and three major distortion errors on the Benton VFDT, scoring 13 out of a possible 32. Additionally, RB was moderately impaired on the Benton Face task, scoring 38 out of a possible 54.

MTB. MTB was shown to be right hand dominant by the Edinburgh Handedness Inventory, and was able to pantomime general tool use. She was unable to identify stereograms at less than 200 arcsec. While this would be considered moderately stereoimpaired in young subjects, Zaroff and colleagues (2003) have shown that stereoacuity decreases with age, and healthy subjects over the age of 60 often show similar levels of stereoacuity to MTB. Though

MTB's foveal vision is corrected-to-normal, visual field tests revealed peripheral dysfunction. Specifically, she has almost no vision in her left visual field and a generalised, but far less extreme, loss of sensitivity in her right visual field.

MTB obtained an MMSE score of 30 out of a possible 30 points, which falls within the normal range for healthy populations in her age-group (Crum et al., 1993). MTB obtained a DRS-2 Total Score of 125 out of a possible 144 points (see Table 1.b), which corresponds to an Age-Corrected MOANS Scaled Score of 5 (3-5 percentile range) and indicates a moderately impaired level of performance. Based on her 15 years of formal education, this Total Score corresponds to an Age- and Education-corrected MOANS Scaled Score of 4 (2 percentile range) and indicates a moderately impaired level of performance. Breaking her results down by subtest, we see that MTB was intact for the CONCEPT subtest, having no difficulty identifying similarities and differences between simple shapes in a design or verbally generating abstract similarities between items. However, MTB proved to be impaired on all other DRS-2 subtests. This impairment was mild for ATT and I/P, moderate for MEM, and severe for CONST. On the ATT subtest, MTB scored perfectly for tests of forward and backward digit span, following commands, verbal recognition, pattern matching, and visual memory. Her poor ATT score was driven solely by her inability to accurately scan and identify target letters in an array. On the I/P subtest, MTB was able to generate a list of different things one might find at a supermarket, but showed some difficulty producing alternating hand movements and drawing a repeating square-triangle "ramparts" design. She demonstrated some memory problems, being unsure of the current day of the week and unable to accurately recall sentences she had been asked to remember. However, she was well orientated to her location, the date, month, season, Mayor, etc., and she performed well on tasks of verbal recognition and visual memory. Finally, MTB

scored very poorly on the CONST subtest, proving unable to generate drawings of even the simplest objects or to clearly write her own name.

MTB's median reaction time of 672ms was significantly slower than the average median reaction time for the control group ($p<0.05$). MTB also showed slowed rates compared to controls on the repetitive finger tapping exercise with both hands, producing 15.3 taps/10s with her right hand ($p<0.05$) and 11.8 taps/10s with her left hand ($p<0.05$).

On a basic object counting task, MTB scored very poorly, answering correctly on only 3 of 14 trials. She correctly identified all 18 objects on a basic object naming task, but managed only 3 out of 15 on the Boston Naming task. MTB found the Benton Line Orientation task and the Benton VFDT too difficult to attempt, stating: "everything looks like it's moving […] there're too many lines." She was also severely impaired on the Benton Face task, scoring 29 out of a possible 54.

SS. SS was shown to be right hand dominant by the Edinburgh Handedness Inventory, and was able to pantomime general tool use. SS registered as stereonormal, identifying stereograms at 70 arcsec. A neurologist's report identified that SS suffers from right homonymous upper quadrantanopia, and "a slight problem with visual acuity due to macular degeneration" (Dr. Gomori, personal communication, March, 2009).

SS obtained an MMSE score of 30 out of a possible 30 points, which falls within the normal range for healthy populations in his age-group (Crum et al., 1993). He also obtained a DRS-2 Total Score of 129 out of a possible 144 points (see Table 1.c), which corresponds to an Age-Corrected MOANS Scaled Score of 6 (6-10 percentile range) and indicates a mildly impaired level of performance. Based on his 19 years of formal education, this Total Score corresponds to

Table 1.c. *DRS-2 Summary Table for patient SS*

Scale/Subscale	Raw Score	Age-Corrected MOANS Scaled Score (AMSS)	Age- and Education-Corrected MOANS Scaled Score (AEMSS)	Percentile Range
Attention	33	7		11-18
Initiation/Perseveration	32	6		6-10
Construction	3	3		1
Conceptualisation	37	10		41-59
Memory	24	10		41-59
DRS-2 Total Score	129	6	4	2

Table 1.d. *DRS-2 Summary Table for patient AP*

Scale/Subscale	Raw Score	Age-Corrected MOANS Scaled Score (AMSS)	Age- and Education-Corrected MOANS Scaled Score (AEMSS)	Percentile Range
Attention	34	8		19-28
Initiation/Perseveration	37	12		72-81
Construction	4	5		3-5
Conceptualisation	37	10		41-59
Memory	21	7		11-18
DRS-2 Total Score	133	9	8	19-28

an Age- and Education-corrected MOANS Scaled Score of 4 (2 percentile range) and indicates a moderately impaired level of performance. Breaking down SS's score by subtest, he proved to be below average, but intact on the CONCEPT and MEM subtests. He correctly identified all 16 pairs of identical and dissimilar objects from an array of objects; generated abstract similarities on a concept formation task; accurately identified his location, the date, season, Mayor, etc.; and performed well on tasks of verbal recall. Conversely, his performance on the ATT and I/P subtests was mildly impaired. On the ATT subtest, SS made minor mistakes on the backwards digit span task and found it difficult to locate target letters mixed in with letters of different sizes and orientation. However, he was able to perform this search task perfectly when the letters were all of the same size and orientation and the array was orderly. SS correctly matched 3 of 4 visual designs, and scored perfectly on a task of visual memory. Conversely, SS was slow to produce a full list of different items found at a supermarket in the I/P subtest, and could not accurately draw a repeating square-triangle "ramparts" design. However, he was perfectly able to produce alternating hand movements, and could draw a simpler repeating "XO" sequence. SS's performance on the CONST subtest was poor, as he was unable to reproduce a drawing of unevenly spaced vertical lines, a diamond in a box, or a square and diamond next to each other. Like RB, it wasn't until the diamond and square were presented individually that SS could produce an accurate recreation of the shapes.

SS's median reaction time of 717ms was significantly slower than the average median reaction time for the control group ($p<0.05$). On the repetitive finger tapping exercise, SS produced 21.5 taps/10s with his right hand and 21.2 taps/10s with his left hand. Like RB, SS's rates of tapping were no different from controls with either hand ($p>0.05$), but his scores clearly fell towards the lower end of the normal scale.

On a basic object counting task, SS scored only 6 out of a possible 14. He correctly identified 8 of 18 objects on a basic object naming task, and 7 out of 15 on the Boston Naming task. He demonstrated severe difficulty on the Benton Line Orientation task, scoring 2 out of 30. SS scored 5 out of a possible 14 on the Benton VFDT, demonstrating one peripheral, one major rotation, and three major distortion errors on the 7 trials attempted. SS was also severely impaired on the Benton Face task, scoring 34 out of a possible 54.

AP. AP was shown to be left hand dominant on the Edinburgh Handedness Inventory, and was able to pantomime general tool use. AP was unable to correctly identify the 'easiest' stereogram at the 400 arcsec level, which indicates a severe deficit in stereoacuity. As previously reported, AP was shown to have mild hemispatial neglect on the right (Dr. P. Shelton, personal communication, December, 2009), but her visual acuity is corrected-to-normal.

AP obtained an MMSE score of 28 out of a possible 30 points, which falls within the normal range for healthy populations in her age-group (Crum et al., 1993). AP obtained a DRS-2 Total Score of 133 out of a possible 144 points (see Table 1.d), which corresponds to an Age-Corrected MOANS Scaled Score of 9 (29-40 percentile range) and indicates a below average, but intact, level of performance. Based on her 16 years of formal education, however, this Total Score corresponds to an Age- and Education-corrected MOANS Scaled Score of 8 (19-28 percentile range) and indicates a mildly impaired level of performance. AP showed normal performance on the I/P subtest, quickly generating a list of things one could find at a supermarket, and readily producing repeating, alternating hand movements. Though she found it difficult and laborious to produce a square-triangle "ramparts" design, she was able to with sufficient accuracy. AP registered as below average, but intact, for the CONCEPT subtest. She correctly identified 14 of 16 pairs of identical and dissimilar objects from an array of objects, and

showed a fully intact ability to generate abstract similarities between items. AP registered as mildly impaired on the ATT and MEM subtests. On the ATT subtest, she struggled slightly with backwards digit span, verbal recognition, and searching and identifying target letters in an array. It should be noted however, that AP scored better than the other three patients in the letter finding task, as she found all six target letters embedded in the ordered array, and only missed one of the five target letters in the randomly ordered display with letters of different sizes and orientations. AP also performed well on tests of visual matching and visual memory for simple designs. AP's score on the MEM subtest was negatively affected by the fact that she thought it was February 1st when tested on January 31st, meaning she got both the date and the month wrong. She also couldn't remember the names of the current Prime Minister or Premier, although she could describe them – in both physical appearance and personality – and state which political parties they represented. Furthermore, she scored perfectly on all other tests of memory: verbal recognition, visual memory, and sentence recall. Finally, as with the other patients, AP was shown to be impaired on the CONST subtest, proving unable to draw unevenly spaced vertical lines or accurately reproduce a picture of a diamond in a box.

AP's median reaction time of 642ms was significantly slower than controls ($p<0.05$). AP's ability to make rapid, repetitive motor movements was also impaired, as she produced fewer finger taps per second than controls during the repetitive finger tapping exercise, producing 5.75 taps/10s with her non-dominant right hand compared to controls' non-dominant hands ($p<0.05$) and 14.25 taps/10s with her dominant left hand compared to controls' dominant hands ($p<0.05$).

On a basic object counting task, AP scored 11 out of a possible 14. She correctly identified all 18 objects on a basic object naming task, as well as 14 of the 15 items on the

Boston Naming task. She found the Benton Line Orientation task difficult, correctly matching lines on 7 of the 15 test items attempted. AP scored 19 out of a possible 32 on the Benton VFDT, demonstrating one peripheral, four major rotation, and two major distortion errors. Conversely, AP fell within the normal range on the Benton Face task, scoring 45 out of a possible 54 points.

Discussion.

RB. The battery of basic testing revealed changes in RB's performance compared to that seen on her initial visits to our lab and to Dr. Shelton in 2008. Her score on the Boston Naming task dropped from 5/15 in 2008 to only 1/15 in 2010. Meanwhile, her score on the Benton VFDT dropped from 20/32 to 13/32 during the same period. Her ability to count the number of objects in a display remained relatively good, although she still made errors, counting correctly in 12/14 of the images in 2010 compared to 13/14 in 2008. Her ability to recognise faces remained impaired, and she was completely unable to match the orientation of lines. Clearly then, RB's perceptual symptoms are becoming more severe as her disease progresses.

Despite her worsening visual problems, RB's executive facilities remain relatively intact. During testing, she was lucid, cogent, amicable, and fully aware of her situation. In line with these observations, RB's performance on the MMSE was within normal limits, and the DRS-2 showed that she performs well on tests of working memory, complex verbal initiation, abstract reasoning, situational orientation, and verbal and visual recall and recognition. Though RB's Total Score on the DRS-2 indicates that her cognitive functioning is moderately impaired, it is clear that her poor performance was driven by perceptual and visuomotor deficits on tasks that require: copying simple visual designs, identifying dissimilar objects from an array, and visually scanning and identifying target letters in an array. However, RB showed slowed reflexes and a trend towards producing slower repetitive finger movements, behaviours that may indicate a

general decline in cognitive functioning. It is possible, then, that RB's progressive atrophy is no longer restricted to posterior, visual processing areas, but is now affecting more anterior portions of her cortex.

MTB. Like RB, MTB showed a decrease in overall perceptual abilities between our first meeting in 2009 and when the current testing was performed in late 2010. For example, MTB's score on the Boston Naming task dropped dramatically from a perfect 15/15 in 2009, to only 3/15 in 2010. Interestingly, despite this poor performance on the Boston Naming task, she correctly identified all 18 objects on a basic object identification task. One major difference between these two tasks is that the Boston Naming task is made up of black-and-white line drawings, while our object identification task uses real, full-colour stimulus images. Additionally, the Boston Naming task includes stimuli that are likely not encountered on a regular basis – such as a beaver and a hammock, while our object identification task uses mainly images of everyday objects – such a fork and a telephone. These differences may explain MTB's superior performance on the object identification test versus the Boston Naming test. In particular, MTB may rely more on the colour or visual texture of objects for identification, rather than their shape or general outline. MTB's score on the object counting test also decreased between testing sessions, as she counted correctly on 7/14 images in 2009 compared to only 3/14 images in 2010. Furthermore, her perceptual deficits are not limited to tests of object recognition, as she was severely impaired on the Benton Face Task and couldn't even attempt tests of line orientation or abstract shape comparison. Based on her own testimony, these deficits seem to be driven in part by constant perceived stimulus motion when she tries to focus on printed images.

Though MTB performed well on the MMSE, her Total Score on the DRS-2 indicates moderately impaired overall cognitive functioning. For the most part, it seems that MTB's poor score was driven by visual perception and graphomotor deficits, as she struggled with scanning and identifying target letters in an array, recreating simple shapes and designs, and writing her name. However, her problems are not entirely visual; she performed poorly on tests of verbal recall and was impaired at producing repeated alternating hand movements. Despite these results, it is clear that her perceptual abilities have not been completely eroded, as she was still able to compare and contrast simple shapes, match patterns, and recognise previously seen designs. As such, it is hard to say whether MTB's poor DRS-2 score was a result of her perceptual deficits or indicative of a more general cognitive decline. In support of the latter conclusion are the results from the reaction time and repetitive finger tapping tasks, on which MTB was significantly slower than controls. Whichever the case may be, it is apparent that MTB's perceptual and graphomotor deficits outweigh her other cognitive issues.

SS. The perceptual difficulties demonstrated by SS on his first visit to Dr. P. Shelton in late 2009 were readily apparent during our testing in late 2010. SS's score of 8/18 on our basic object naming and 7/15 on the Boston Naming task are comparable to, or perhaps slightly worse than, his performance in 2009, where he scored 19/30 on tests of object recognition and naming. Similarly, SS showed severe deficits in face recognition when tested in 2009 and again in 2010. SS's very poor scores on tests of complex figure copying, clock drawing, and object cancellation in 2009 combined with his difficulties on tests of object counting, visual form discrimination, and line orientation matching in 2010, are indicative of profound perceptual and visuospatial dysfunction.

SS made no errors on the MMSE, but his performance on the DRS-2 was less than perfect; his Age- and Education- corrected score indicates a moderately impaired level of performance. Like RB and MTB, SS showed the most difficulty with tasks that require him to copy designs that include more than one very simple shape at a time, or to visually scan an array to locate target letters. Though his poor DRS-2 score was mainly driven by his performance on these types of tasks, he also made mistakes in backwards list repetition and rapid list generation. These results suggest that SS may be dealing with more extensive cognitive problems than just visuomotor and perceptual dysfunction. In support of this conclusion is the fact that SS's simple reaction time is significantly slower than controls. However, SS's overall cognitive capabilities are still relatively intact, given his good situational awareness, ability to generate abstract similarities between objects, and normal repetitive finger tapping speeds.

AP. AP's perceptual deficits do not seem nearly as pronounced as the other three PCA patients. For example, she scored very well on tests of face and object naming and recognition. These abilities were apparent in late 2009, when she visited Dr. P. Shelton, and remained intact in late 2010, when she performed very well on our object naming task, the Boston Naming task, and the Benton Face task. AP did struggle on certain perceptual tasks, however, such as the Benton Line Orientation task and the Benton VFDT. It can be argued that these two tasks are more challenging than simply naming objects or faces. Indeed, control subjects often reported that these tasks required more effort and concentration. Additionally, the Benton VFDT and Line Orientation task require participants to match test shapes to a target shape embedded in an array of distractors. As such, these tasks are far more susceptible to errors in trans-saccadic memory and simultanagnosia. It is possible that AP's poor performance is being driven by such deficits. Indeed, Dr. P. Shelton noted that AP showed problems indicative of simultanagnosia, and we have seen that she is susceptible to making errors on basic object counting tasks.

AP scored quite well on tests of general cognitive ability, but fell into the mildly impaired category for the DRS-2 once her academic history was taken into account. Like the other three patients, AP's major issue seems to be her inability to reproduce designs that are any more complex than a simple, isolated shape. Her ability to search and identify target letters in an array was better than the other patients, though not perfect, and she only made minor mistakes in discerning similar from dissimilar objects. As was explained in the Results section, her poor performance on the memory subtest didn't seem indicative of genuine memory impairment, although she did show some difficulty on tests of backwards digit span repetition and verbal memory. Finally, AP had significantly slower reaction times and repetitive finger tapping rates than controls, which may be indicative of general cognitive decline. However, it should be noted that AP, on her visit to Dr. P. Shelton in 2009, demonstrated mild increases in muscle tone and slowed limb movements (bradykinesia), which likely had a negative influence on her reaction time and finger tapping performance.

Study I: Delayed Grasping

Background. When we reach out to grasp an object, our fingers and hand 'anticipate' the upcoming interaction by preparing for contact during the initial reaching stage of the movement. As we make proximal (arm) movements to transport our hand to the object's location, we also make distal (wrist, hand, and finger) movements that reflect the geometric properties of the target object. For example, our wrist and lower arm rotate to align the hand with the required orientation for object interaction, and our fingers open wide enough to be able to execute a grasp. Grip aperture in a precision grasp – using only the index finger and thumb – is the distance between these two effector fingers. In a normal reach-to-grasp movement, grip aperture reaches a maximal value – maximum grip aperture (MGA) – 60-80% of

the way through the reach (Jeannerod, 1984; Gentilucci et al., 1991). Importantly, MGA has been shown to exhibit a reliable, positive correlation with the size of the object to be grasped (Paulignan, MacKenzie, Marteniuk & Jeannerod, 1990). In this way, MGA is a useful measure of proper visuomotor functioning.

The higher-order visual deficits seen in PCA seem to result from damage to both the dorsal and ventral streams. However, in some patients, the damage to one stream is predominant, and the extent to which each neural pathway is affected varies between patients. This variation in both the location of neural degeneration and the type and extent of deficits exhibited by PCA patients provides an opportunity to explore the subtleties of the dissociation between the cortical guidance of vision for action and vision for perception. Delayed grasping has surfaced as a useful tool for distinguishing between the dorsal and ventral control of a motor task. Goodale, Jakobson, and Keillor (1994) showed that grasp kinematics change when participants are asked to pantomime a grasp to a remembered object following a delay compared to visually guided grasps to that same object. Specifically, they found that pantomimed grasps reach a lower peak velocity (something that may be due, in part, to reduced absolute reach amplitudes), produce smaller overall peak grip apertures, and increase the relative time to peak grip aperture. The authors suggest that this change in kinematics results from a shift in the neural control of the action from real time visuomotor control systems in the dorsal stream to stored perceptual object representations in the ventral stream. They supported this conclusion by testing DF, a patient with profound perceptual deficits due to bilateral damage to her ventral stream (Milner et al., 1991; Murphy, Carey, & Goodale, 1998). Even though DF could perform the real time grasping task without problem (Goodale, Milner, Jakobson, & Carey, 1991; Goodale et al., 1994a), her ability to properly scale her grip when performing a grasp following a delay was almost completely eliminated (Goodale et al., 1994a).

Important complimentary evidence was provided by Milner and colleagues (2003) who demonstrated that optic ataxic patients, who cannot properly scale their grip during visually guided movements due to dorsal stream damage, regain this ability when presented with a delayed grasping task.

Other investigators have produced similar findings using pointing tasks. A number of groups have shown that introducing a delay into a pointing task produces a significant improvement in pointing accuracy for optic ataxic patients (Himmelbach & Karnath, 2005; Milner, Paulignan, Dijkerman, Michel, & Jeannerod, 1999; Revol et al., 2003; Milner et al., 2001). Conversely, patient DF produces much larger errors than controls when pointing after a delay compared to her excellent performance on the same task in real time (Milner et al., 1999b). This double dissociation between dorsal and ventral stream damage and the ability to perform accurate delayed motor tasks, provides attractive support for Goodale et al.'s (1991; 1994) theory that delayed grasping relies on a different cortical system than real time grasping. Furthermore, evidence from these studies agrees with Goodale and Milner's supposition that the dorsal stream is specialised for the online control of object interaction, while the ventral stream codes object characteristics into longer memory representations.

Methods. This first study used the delayed grasping task as a means of comparing the respective loss of function in the dorsal and ventral visual areas of our patients. The task consisted of three conditions: closed-loop grasping, immediate open-loop grasping, and delayed open-loop grasping. In the closed-loop condition, participants were able to reach out and pick up a single object with visual feedback of their actions fully available. In immediate open-loop grasping, participants were allowed to view the target object for three seconds before being given a cue-to-grasp as their vision was occluded. It has been argued that immediate open-loop

grasping does not necessarily rely completely on either visuomotor systems or on perceptual information, but rather on both as the visuomotor system transitions from using incoming visual information to stored perceptual information (Himmelbach and Karnath, 2005). In delayed open-loop grasping, participants were first allowed to view the target object for three seconds before their vision was occluded. Once their vision was removed, they were required to wait three seconds before the auditory cue-to-grasp was presented. Trials were blocked by condition, and the order in which conditions were performed was counterbalanced across participants.

In each of the three viewing conditions, symmetrical 'Efron blocks' were placed on a tabletop in front of participants at their midline. Participants were provided with a 'start button' – a raised landmark 7cm from the edge of the table – to which they were instructed to return their hand after each grasp. Between all trials, participants were told to keep their index finger and thumb together and resting on the start button, with their remaining fingers tucked comfortably against their palm. An auditory cue-to-grasp – a brief tone – indicated the start of each trial, at which point participants were free to initiate a grasp movement. Participants were required to execute a precision grasp – using only their index finger and thumb in opposition – to each object, grasping the blocks across their vertical axis. Efron blocks are small, rectangular, wooden objects with the same overall surface area but different geometric dimensions. Five different sized Efron blocks were used for this study: block A (length: 5.0 cm, width: 5.0 cm, height: 1.1 cm), block B (length: 5.3 cm, width: 4.5 cm, height, 1.1 cm), block C (length: 6.3 cm, width: 4.0 cm, height: 1.1 cm), block D (length: 7.2 cm, width: 3.5 cm, height: 1.1 cm), and block E (length: 8.0 cm, width: 3.0 cm, height: 1.1 cm). However, blocks B and D served as distracters, and only the data from blocks A, C, and E was analysed. Distracter blocks were employed to reduce the chance that participants might learn to employ a conscious strategy to their

grasping, such as 'ball-parking': "Oh, that's the medium-sized one". Blocks were placed on the tabletop directly in front of participants, and were centered at one of three distances: 20cm, 30cm, or 40cm from the edge of the table. Each of the target blocks – A, C, and E – was presented 15 times in each condition – five times at each of the three distances, while the distracter blocks – B and D – were presented six times – twice at each of the three distances. In total, participants made 57 grasps for each of the three conditions, for a total of 171 trials per testing session.

Position and velocity recordings were made using a portable Motion Monitor system (Innovative sports technology; Chicago) attached to magnetic sensors. Individual sensors were attached to the index finger, thumb, and wrist of each participant's dominant hand. This setup allowed for the measurement of grasp kinematics, including MGA and peak wrist velocity. The Motion Monitor system also provided temporal information, allowing for the extraction of variables such as time-to-MGA, time-to-peak velocity, and movement duration. Of primary importance for this study was MGA, which demonstrated whether or not PCA patients show normal grip scaling based on object size, as compared to controls. For this task, participants wore 'shutter goggles' (*PLATO* Translucent Technologies, Toronto) over their regular eye-wear (if any), which could be remotely toggled between a transparent and an opaque state. Custom-written software, run off the Motion Monitor system, allowed for the timing of visual occlusion to be precisely controlled. The presentation of the auditory tone, used as the cue-to-grasp, was controlled by the same software responsible for switching the shutter goggles. As a result, the timing of the grasp-cue and visual occlusion was precisely controlled in all conditions.

Analysis. Finger position data from the magnetic sensors was captured by Motion Monitor software. This software was programmed to calculate grip aperture by determining the

length of the vector between the coordinates of the index finger and thumb positions. Custom-written algorithms in Motion Monitor outputted the value of MGA for each grasp. A separate regression analysis was run for each participant under each condition (closed-loop, immediate, and delayed). This analysis was able to reveal whether participants' grip apertures were scaled in relation to the size of the block, as shown by a regression slope significantly different from zero. To determine whether patients' scaling behaviour was comparable to controls, a 95% confidence interval was generated for the mean Fisher transformed correlation coefficient for each condition. Patients' correlation values were then compared to these confidence intervals; values falling outside the confidence interval indicated that a patient's scaling behaviour was different from that of the controls. This comparison was only performed for conditions in which patients actually demonstrated significant scaling behaviour.

In addition to MGA, four other kinematic variables were measured and analysed for this study: time-to-MGA, peak velocity, time-to-peak velocity, and movement duration. 'Time-to-MGA' was the time it took for MGA to be achieved following movement onset. 'Peak velocity' was simply the maximum forward velocity reached by the wrist throughout the course of the reach-to-grasp movement. 'Time-to-peak velocity', like time-to-MGA, was the time between movement onset and peak wrist velocity. 'Movement duration' was simply defined as the total time taken to complete the grasp. The timing of the reach commenced at 'movement onset' – the time at which forward wrist velocity exceeds 0.05 m/s, and object contact – signified by the end of the trial. In order to compare the behaviour of patients to that of controls, a 95% confidence interval was generated surrounding the mean value for each condition. Individual patient data was then plotted against these confidence intervals to determine if patients were performing in a different manner compared to controls. Additionally, single-subject ANOVAs were run for each patient to test for significant differences across conditions for each variable.

These ANOVAs allowed us to determine whether the changes in condition had similar effects on the patients as compared to the control group. Post hoc analysis using Tukey's Honestly Significant Difference (Tukey's HSD) test determined the exact 'location' of any main effects.

Results.

When presented with blocks at their midline under closed-loop (free-viewing) conditions, all controls demonstrated appropriate grip scaling with respect to the height of the block, as shown by negatively sloped regression lines that were significantly different from zero (see Table 2.a). Conversely, RB showed no evidence of scaling for this same condition (r^2=0.048; F[1,43]=2.134, p=0.152). Meanwhile, MTB, SS, and AP all demonstrated scaling behavior (MTB: r^2=0.444; F[34.379, p<0.001; SS: r^2=0.232; F[1,43]=12.986, p=0.001; AP: r^2=0.295; F[1,43]=18.022, p<0.001). In addition to showing scaling, MTB and AP's grasps were no different than controls (p>0.05), while SS's scaling was slightly weaker than controls (p<0.05; see Figure 1).

In the immediate (open-loop) condition, all controls once again showed appropriate scaling (see Table 2.b). SS and AP also showed significant scaling behavior (SS: r^2=0.260; F[1,43]=14.734, p<0.001; AP: r^2=0.128; F[1,44]=6.292, p=0.016), which was no different from controls (p>0.05; see Figure 1). Meanwhile, RB and MTB showed no evidence of scaling in the immediate open-loop condition (RB: r^2=0.032; F[1,43]=1.405, p=0.243; MTB: r^2=0.002; F[1,40]=0.088, p=0.768).

Finally, when a delay was introduced between object viewing and movement onset, all four patients failed to show appropriate grip scaling (RB: r^2=0.090; F[1,42]=4.076, p=0.050; MTB: r^2=0.027; F[1,39]=1.045, p=0.313; SS: r^2=0.048; F[1,44]=2.190, p=0.146; AP: r^2=0.019;

Table 2.a. *Regression values for Closed-loop grasping*

	Slope	R^2	p-value
RB	-3.004	.048	0.152
MTB	-9.2	.444	<0.001
SS	-5.2	.232	0.001
AP	-3.633	.295	<0.001
Control I (II)	-5.467	.634	<0.001
Control II (GI)	-4.533	.395	<0.001
Control III (KS)	-9.467	.599	<0.001
Control IV (SF)	-7.267	.728	<0.001
Control V (TS)	-9.933	.622	<0.001
Control VI (BH)	-8.767	.846	<0.001
Control VII (SJ)	-6.642	.507	<0.001
Control VIII (VD)	-5.583	.477	<0.001

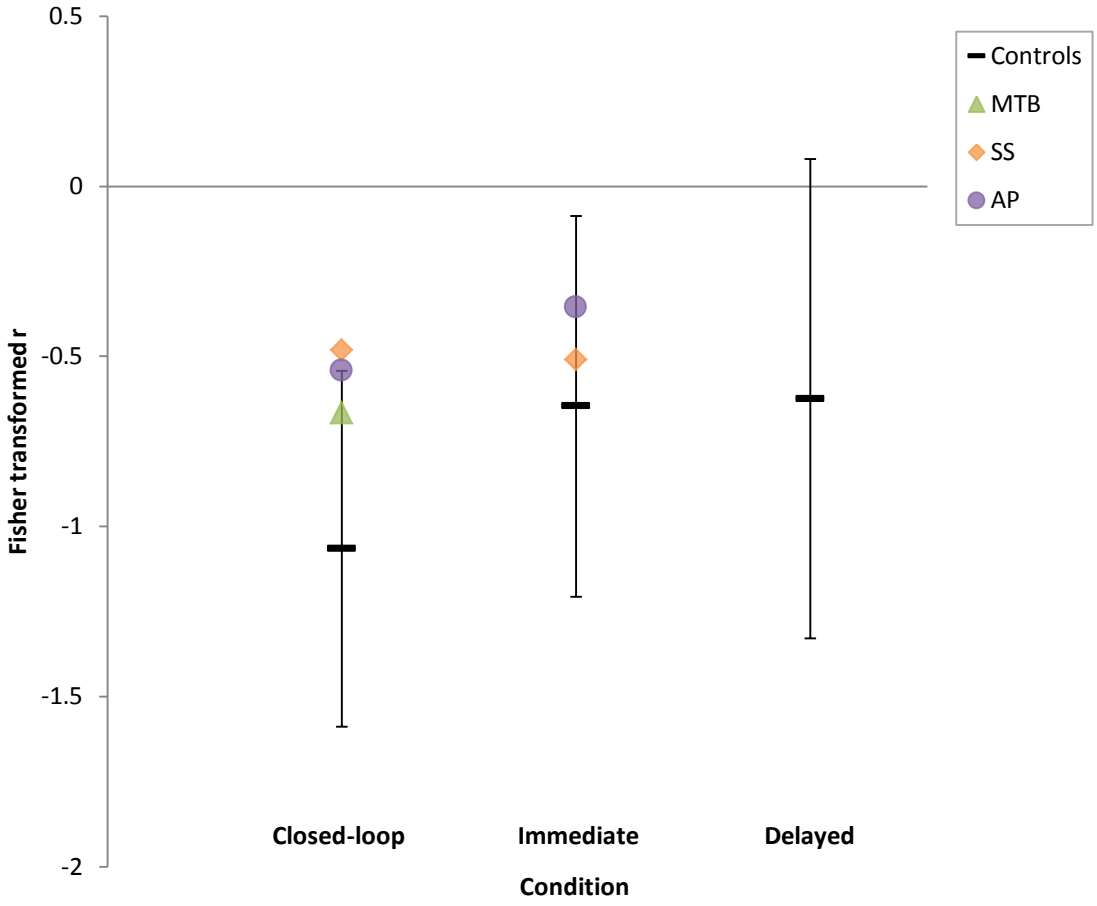
Table 2.b. *Regression values for Immediate Open-loop grasping*

	Slope	R^2	p-value
RB	1.532	.032	.243
MTB	-.500	.002	.768
SS	-7.040	.260	<0.001
AP	-3.067	.128	.016
Control I (II)	-4.467	.452	<0.001
Control II (GI)	-3.167	.125	.017
Control III (KS)	-4.467	.263	<0.001
Control IV (SF)	-4.200	.207	0.002
Control V (TS)	-5.967	.232	0.001
Control VI (BH)	-10.267	.724	<0.001
Control VII (SJ)	-5.300	.360	<0.001
Control VIII (VD)	-4.233	.165	0.006

Table 2.c. *Regression values for Delayed Open-loop grasping*

	Slope	R^2	p-value
RB	2.321	.090	.050
MTB	-1.500	.027	.313
SS	-2.733	.048	.146
AP	1.100	.019	.373
Control I (II)	-5.833	.477	<0.001
Control II (GI)	-1.600	.105	.030
Control III (KS)	-5.367	.292	<0.001
Control IV (SF)	-2.633	.115	0.023
Control V (TS)	-5.900	.352	<0.001
Control VI (BH)	-6.667	.746	<0.001
Control VII (SJ)	-1.300	.025	0.304
Control VIII (VD)	-3.800	.371	<0.001

Figure 1. *Correlation coefficients for grip scaling in Study I*



Note. Data points represent the Fisher transformed r values from a regression analysis comparing MGA to block size for each of the three conditions in Study I. Coefficients are only included for participants who demonstrated scaling behaviour that was significantly different from zero, hence the absence of patient data for the delayed condition. The error bars for the control data represent a 95% confidence interval.

F[1,44]=0.811, p=0..373). Meanwhile, seven out of eight controls showed evidence of grip scaling in this condition (see Table 2.c). Interestingly, while MTB, SS, and AP showed no evidence of scaling, RB did demonstrate significant scaling (p=0.05), but in the opposite direction to what was expected. In other words, her maximum grip aperture increased as the height of the block decreased.

Controls showed a significant change in overall MGA across conditions (F[2,1064]=80.619, p<0.001; see Figure 2.a). As might be expected when removing visual feedback of the reach, post hoc analysis revealed significantly larger overall MGAs during the open-loop conditions (immediate: 9.77cm; delayed: 9.93cm) compared to the closed-loop condition (8.87cm; p<0.001). There was no difference between the immediate and delayed open-loop conditions (p=0.165). Similarly, controls showed changes in time-to-MGA across conditions (F[2,1061]=29.729, p<0.001; see Figure 2.b). This change manifested in an increased temporal latency between movement onset and MGA between closed-loop (0.47s) and immediate open-loop grasping (0.55s; p<0.001), as well between immediate and delayed open-loop conditions (0.61s; p=0.003). Controls also showed changes in peak velocity across conditions (F[2,1062]=43.163, p<0.001; see Figure 2.c), with an opposite pattern to MGA: peak velocity having a lower amplitude during the two open-loop conditions (immediate: 67.39m/s; delayed: 66.31m/s) compared to the closed-loop condition (78.71m/s, p<0.001). There was no difference in peak velocity between immediate and delayed open-loop grasping (p=0.742). The time it took for controls participants to reach peak velocity also differed across conditions (F[2,1062]=43.163, p<0.001; see Figure 2.d). Like time-to-MGA, time-to-peak velocity was protracted during open-loop grasping (immediate: 0.24s; delayed: 0,25s) compared to the closed-loop condition (0.21s, p<0.001). Once again, there was no difference between immediate

Figure 2.a. *Maximum Grip Aperture across conditions in Study I*

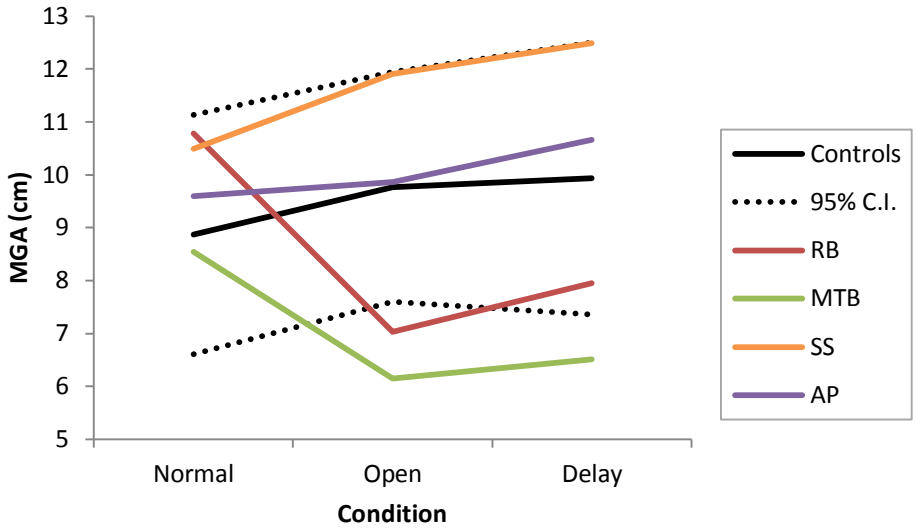


Figure 2.b. *Time to MGA across conditions in Study I*

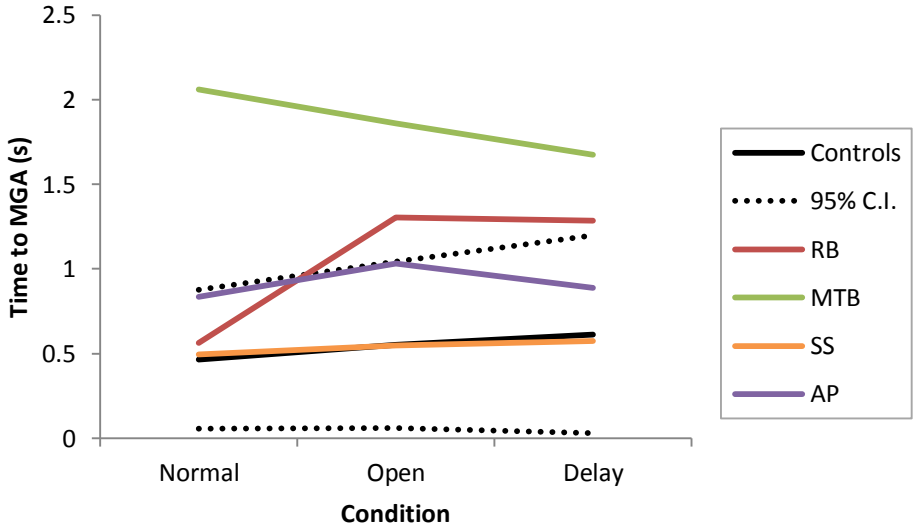


Figure 2.c. *Peak Velocity across conditions in Study I*

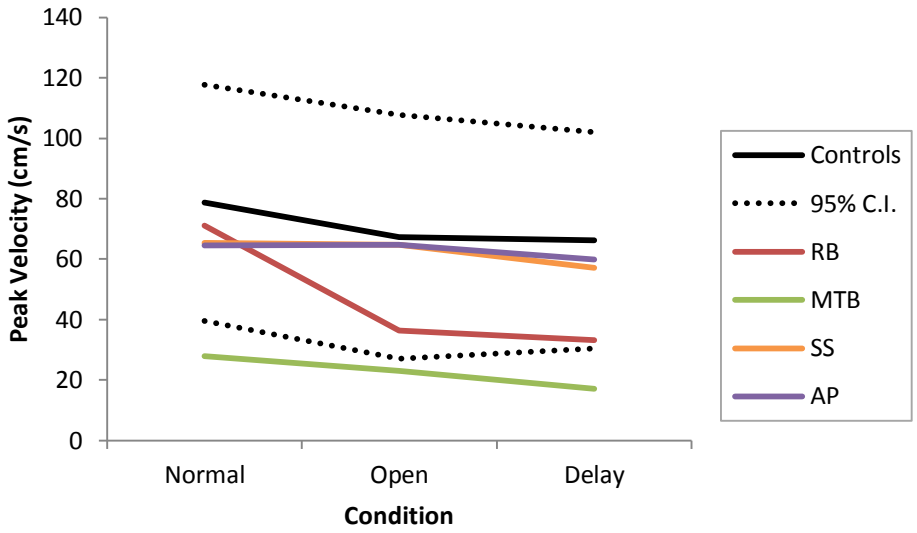


Figure 2.d. *Time to Peek Velocity across conditions in Study I*

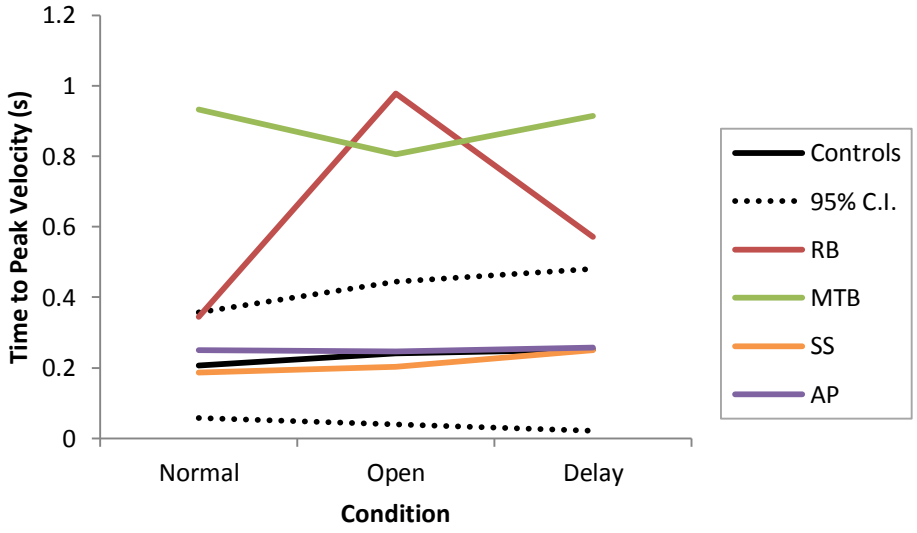
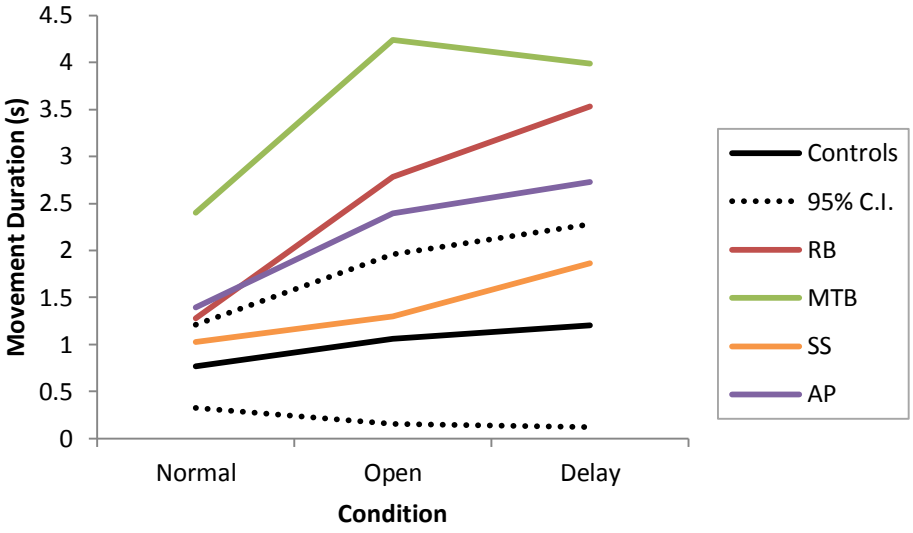


Figure 2.e. *Total Movement Duration across conditions in Study I*



and delayed open-loop conditions ($p=0.416$). Additionally, the overall length of the reach changed across conditions ($F[2,1067]=91.874$, $p<0.001$; see Figure 2.e). Movement duration increased from closed-loop (0.77s) to immediate open-loop grasping (1.06s, $p<0.001$), as well as from immediate to delayed open-loop grasping (1.20s, $p<0.001$).

A direct statistical comparison cannot be made regarding overall MGA values between patients and controls, due to finger size presenting as a confounding variable. However, we can look at the pattern of change between conditions within individual patients and compare that change to controls. Figure 2.a shows a graphical illustration of the previously reported control data along with that of the patients. As we saw previously, controls showed a significant increase in overall MGA in the open-loop conditions compared to closed-loop. It is interesting to see that SS and AP showed a very similar pattern of behaviour to controls, while RB and MTB's results strike a dramatic contrast. SS's MGA values increased steadily across conditions from 10.49cm in the closed-loop condition, to 11.90cm in the immediate condition, and 12.48cm in the delayed condition ($F[2,133]=44.449$; $p<0.001$). AP showed a similar pattern, with MGAs of 9.59cm, 9.87cm, and 10.66cm, in the respective conditions ($F[2,134]=33.872$; $p<0.001$). RB and MTB's results were very different. RB's overall MGA dropped hugely from 10.78cm in the closed-loop condition, to 7.03cm and 7.95cm in immediate and delayed conditions, respectively ($F[2,131]=234.193$; $p<0.001$). Meanwhile, MTB's overall MGA dropped from 8.55cm to 6.14cm and 6.51cm for those same conditions ($F[2,125]=79.937$; $p<0.001$). As might be expected from looking at the numbers, post hoc analysis revealed that these main effects of condition for RB and MTB were driven mainly by significant differences in overall MGA between the closed-loop condition and both open-loop conditions, rather than between the two open-loop conditions. However, it should be noted that RB's overall MGAs actually increased significantly between the immediate and delayed conditions ($p<0.001$).

Figure 2.b shows a comparison of the time taken to reach MGA across conditions. SS showed very similar actual time values to controls, falling well within the 95% confidence interval of control data. He also demonstrated a pattern of increasing time to MGA from closed-loop to open-loop conditions, although this increase was not significant ($F[2,133]=2.972$; $p=0.055$). AP showed a pattern of longer time to MGAs than controls across all conditions, but this difference was not significant for any one condition ($p>0.05$). AP also demonstrated a significant change in time-to-MGA across conditions ($F[2,134]=4.844$; $p=0.009$). Post hoc analysis revealed this difference was driven by a significant increase in time-to-MGA between closed-loop and immediate open-loop grasping ($p=0.009$), with no significant difference between the two open-loop conditions, or indeed closed-loop and delayed ($p>0.05$). MTB, on the other hand, demonstrated a significantly longer time-to-MGA than controls across all three conditions ($p<0.05$). She also showed a pattern of decreasing time-to-MGA from closed- to open-loop conditions, but this change was not significant ($F[2,125]=2.139$; $p=0.122$). RB's time-to-MGA was comparable to controls in the closed-loop condition, but significantly longer in both open-loop conditions ($p<0.05$). This difference was driven by a large increase in time-to-MGA between the closed-loop and open-loop conditions ($F[2,130]=24.623$; $p<0.001$).

Figure 2.c showed the data for peak wrist velocity. SS and AP again showed very similar results to each other as well as to controls – their data falling well within the 95% confidence interval of control data for all conditions. Like controls, SS's peak velocity decreased across conditions from 65.43m/s in closed-loop grasping to 64.83m/s in the immediate condition, and then 57.22m/s in the delayed condition ($F[2,134]=3.441$, $p=0.035$). AP showed very similar peak velocities to SS, with values of 64.45m/s, 64.85m/s, and 59.84m/s across the respective conditions, but these differences were not significant ($F[2,134]=2.353$, $p=0.099$). RB showed a more dramatic decrease in velocity between the closed and open-loop conditions, with her peak

velocity falling from 71.20m/s in the closed-loop condition to 36.32m/s and then 33.31m/s for immediate and delayed grasping ($F[2,133]=89.651$, $p<.001$). Despite this large decrease in peak velocity for the open-loop conditions, RB's speeds fell within the 95% confidence interval of control data, and were therefore no different from controls, though she came very close to being different in the delayed condition. Finally, MTB showed significantly lower peak velocities than controls across all three conditions ($p<0.05$), with velocities of 27.90m/s, 22.99m/s, and 17.17m/s. Regardless of her overall much slower velocities, MTB still showed the same pattern of decreasing peak velocity across conditions ($F[2,134]=24.812$, $p<0.001$).

As we can see from Figure 2.d, SS and AP once again showed very similar results to controls; their time-to-peak velocity results matched those of controls almost perfectly ($p>0.05$). While AP showed no significant change in time-to-peak velocity across conditions ($F[2,134]=0.265$, $p=0.768$), SS demonstrated a slight increase ($F[2,134]=3.538$, $p=0.032$). Post hoc analysis revealed this difference to be driven by an increase in time-to-peak velocity between the closed-loop condition and the delayed condition ($p=0.031$). As with peak velocity itself, RB showed a large change in her kinematic behaviour between closed- and open-loop grasping when it comes to the timing of her peak velocity. It took RB an average of 0.35s to reach her peak velocity in the closed-loop condition, which, although very close, was not significantly slower than controls ($p>0.05$). However, this timing increased significantly to 0.98s and 0.57s for immediate and delayed grasping ($F[2,133]=14.397$, $p<0.001$), respectively, both of which were slower than controls ($p<0.05$). As with the timing of her MGA, MTB once again showed much longer intervals from movement onset to peak velocity across all conditions as compared to controls ($p<0.05$). The time it took MTB to reach peak velocity was not different across conditions ($F[2,134]=0.563$, $p=0.571$).

Figure 2.e shows the overall movement durations across conditions for all subjects. Here, SS was the only patient whose kinematics were comparable to controls. Like controls, SS showed a pattern of increasing durations across conditions: 1.03s, 1.30s, and 1.86s, respectively ($F[2,134]=16.085$, $p<0.001$). While movement durations were slightly slower than controls for all conditions, they were not significantly different ($p>0.05$). The other three patients: RB, MTB, and AP, all showed much longer overall movement durations than controls for all conditions ($p<0.05$). All three patients also showed large increases in movement duration in the open-loop conditions compared to closed-loop grasping (RB: $F[2,134]=46.675$, $p<0.001$; MTB: $F[2,134]=17.573$, $p<0.001$; AP: $F[2,134]=32.040$, $p<0.001$).

The increase in overall movement duration seen above was likely due to the large increase in the number of grasp corrections made by the patients in the open-loop conditions. Figure 3 represents how successful controls and patients were at accurately guiding their hand and fingers to the target block in each condition. This accuracy was measured by categorising each grasp as either 'successful' – hand was directed to the correct target location and the grasp was executed without corrections having to be made; 'missed grasp' – hand was directed to the correct target location, but corrections were required to acquire a stable grasp; and 'missed block' – hand was not directed to the correct target location. Looking first at control data (see Figure 3.a), we can see that healthy participants had no trouble performing an accurate grasp under visual guidance, as would be expected, making accurate, uncorrected grasps 99.2% of the time. Their performance decreased slightly when vision was obscured, but still remained relatively precise, making accurate grasps 87.5% and 84.4% of the time in the immediate and delayed conditions, respectively. When grasps were not accurate in these conditions, it was most common for mistakes to consist of minor grip adjustments following object contact. Complete misses were rare (immediate: 0.3% and delayed: 1.7%).

Figure 3.a. *Grasping precision in Study I: Controls*

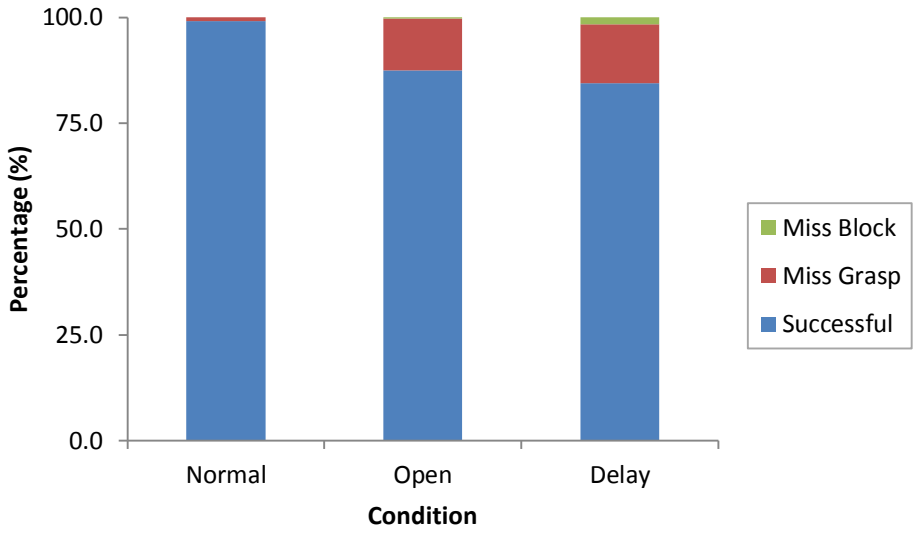


Figure 3.b. *Grasping precision in Study I: RB*

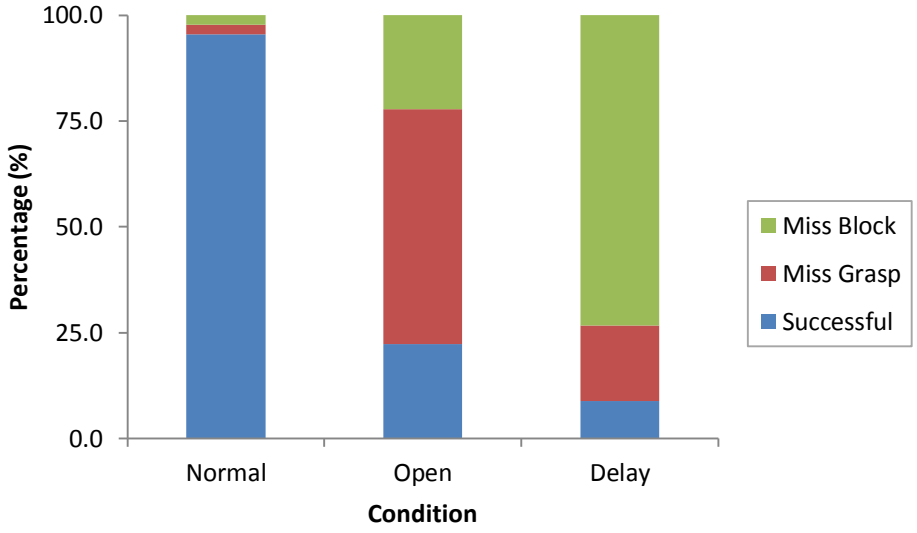


Figure 3.c. *Grasping precision in Study I: MTB*

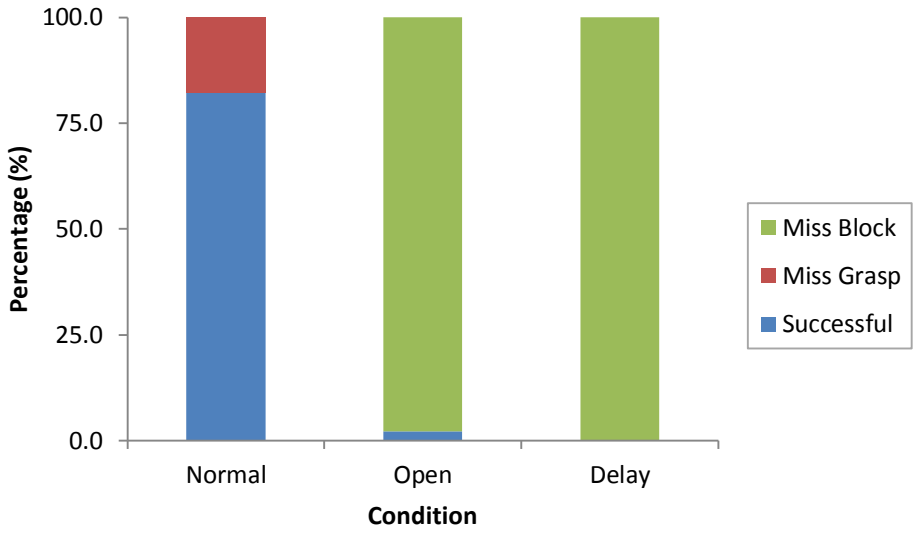


Figure 3.d. *Grasping precision in Study I: SS*

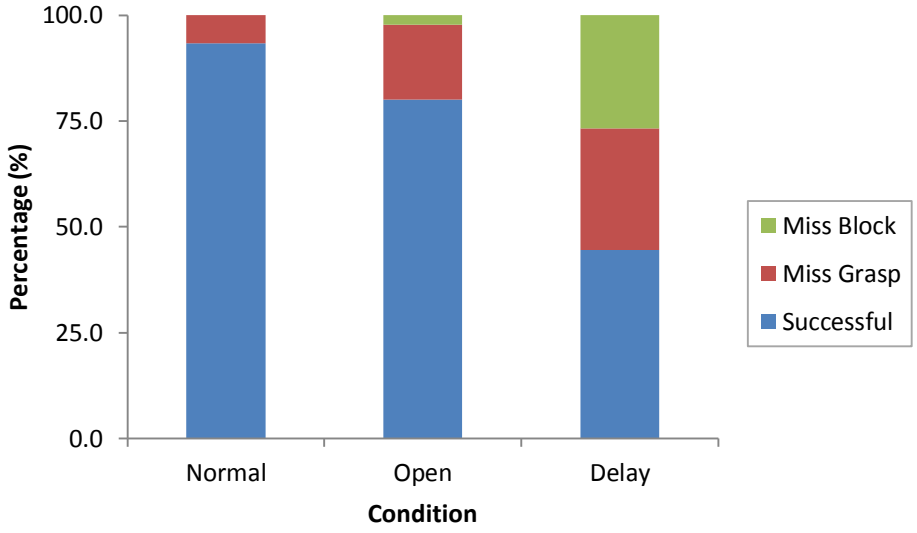
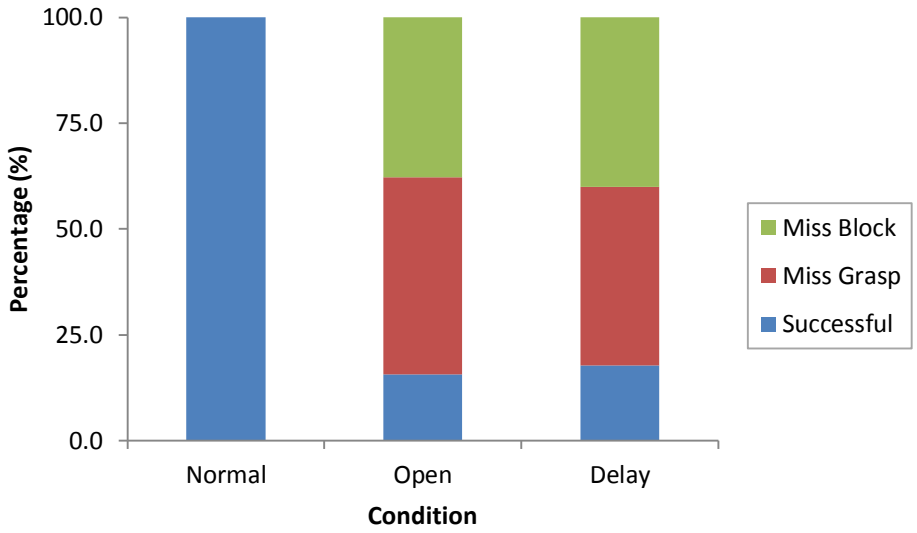


Figure 3.e. *Grasping precision in Study I: AP*



The patients' performances were dramatically different to that of controls. Despite RB's failure to scale her grasps in the closed-loop condition, she was able to guide her fingers to appropriate grasp sites without correction on 95.6% of trials (see Figure 3.b). However, this performance changed greatly in the open-loop conditions, where only 22.2% and 8.9% of her grasps were accurate for immediate and delayed grasping, respectively. What's more, in the delayed condition, RB missed the target object completely on 73.3% of trials. MTB's performance was even less accurate than RB. Despite showing appropriate scaling in the closed-loop condition, MTB made slight grip corrections on the block for 17.8% of grasps (see Figure 3.c). Additionally, she proved unable to locate objects without constant visual feedback of the scene, as she missed the target location on 98.9% of her grasps across both open-loop conditions. SS's performance was noticeably better than RB and MTB. He made corrections on only 6.7% of his closed-loop grasps and 20.0% of his grasps in the immediate condition (see Figure 3.d). However, his delayed performance was poor, as he made minor grip corrections on 28.9% of his grasps and missed the block completely on 26.7%. Finally, AP's performance was more akin to that that of RB and MTB than SS in that she executed accurate grasps on all closed-loop trials, but required minor corrections to 46.7% and 42.2% of her grasps in the immediate and delayed conditions (see Figure 3.e). Furthermore, AP missed the block completely on 37.8% and 40.0% of trials during immediate and delayed grasping, respectively.

Discussion.

RB. RB's failure to scale her grip to the size of the object under free-viewing conditions with the object located at her midline demonstrates a severe breakdown in visuomotor functioning. It can be argued that this situation represents the simplest of conditions in which the visuomotor system is required to function: constant visual feedback of both the effector

hand and the target object is readily available throughout the entire movement, the object is located at the participant's midline, the object is located in central vision without any gaze restraints, and the object is a simple rectangle on which appropriate grasp sites need not be chosen – a grasp across the block's vertical axis at any horizontal location will provide for an adequately stable grip. Yet, even under these most basic of conditions, RB failed to open her fingers significantly wider when approaching a larger target compared to a smaller one.

RB's inability to perform accurately on a simple visuomotor task suggests that she suffers substantial damage to the occipito-parietal cortical areas that control such behaviour. As was discussed earlier, paradoxical improvements in reaching and grasping have previously been reported in patients with optic ataxia who have localised damage to superior parietal cortex. If RB's cortical damage was similarly restricted to, or even primarily located in the parietal lobe, we might expect to see an improvement in her grasping once we removed visual feedback and forced her visuomotor system to rely on a stored percept of the target object retrieved from the ventral stream of visual processing. However, given RB's extensive perceptual deficits, a similar improvement was unlikely in this case. Accordingly, RB's performance was equally poor in the immediate open-loop condition, in which she was allowed to view the target object for three seconds before executing the grasp without visual feedback. In fact, under these conditions RB's grasps produced a positively sloped regression line, albeit one that was not significantly different from zero.

RB's performance remained poor when a three-second delay was introduced between object viewing and movement onset. In this condition, RB's grasps actually produced a positive regression line, the slope of which was significantly different from zero. This indicates an inverse relationship between the magnitude of her maximum grip aperture and the vertical size of the

block. This is an intriguing result. One possible explanation for this behaviour is that RB was scaling her grip based on the horizontal, rather than the vertical, dimension of the block. Such a hypothesis would explain the current behaviour since the thinner the Efron blocks get along the vertical axis, the wider they get along the horizontal axis. However, this explanation leads to an awkward, yet necessary logical conclusion: RB's perceptual system is intact enough to provide accurate target information regarding the horizontal size of the blocks to her visuomotor system, which is, in turn, intact enough to use this information to accurately scale her grasps. Both of these conclusions seem spurious, given RB's performance on basic tests of perceptual functioning and her grasping performance under closed-loop conditions. Some support for this explanation comes from the observation that RB would occasionally execute a grasp to the target object across its horizontal axis. However, these grasps only ever occurred with Block A, and such trials were excluded from the overall analysis.

In addition to RB's failure to properly scale her grasps under any of the three conditions, she demonstrated additional kinematic deficits indicative of impairments to both her visuomotor and perceptual systems. While controls showed a steady increase in MGA from closed-loop to immediate open-loop to delayed grasping, RB showed a sharp decrease in overall MGA in the open-loop conditions compared to the closed-loop situation. This behaviour seems illogical given the task demands. In the closed-loop condition, visual feedback is freely available to participants throughout the grasp. Healthy individuals will use this information to minimise energy expenditure by closely matching their grip size to the actual size of the object, since minor corrections can be made on-line during the reach-to-grasp movement to ensure successful contact is made. Once vision is removed, however, one can no longer rely on real-time information to synchronise the hand and target locations in order to correct slight inaccuracies. To compensate for this lack of information in open-loop conditions, the

visuomotor system exaggerates in-flight grip to minimise the chance of the fingers colliding with the target object. In delayed grasping, uncertainty as to the precise target location increases further, so additional precaution is taken by opening the grasping fingers yet wider. All of this makes logical sense, and this is exactly the behaviour we saw from the control group in this study. It is curious, then, that RB did not perform in a similar fashion, *especially* given her perceptual difficulties. From RB's performance on basic perceptual tasks, it is reasonable to assume that her access to information regarding the location and geometric properties of the target object is severely limited in open-loop conditions. Based in this assumption, one might predict that RB's visuomotor system would program excessively large grip apertures under these conditions to accommodate for the presence of dramatically increased uncertainty. The question then, is why RB did not perform as we might expect. There are a number of possible explanations: Her visuomotor systems may be so damaged that they are no longer capable of making such basic adaptive adjustments in the face of incomplete or nonexistent target information; her visuomotor systems may have lost their connections to higher-order brain centers that would issue a command to over-ride natural, 'automatic' reach behaviours in favour of more conservative strategies; her visuomotor systems may have lost their normal connections to perceptual centers that would warn of an uncertainty in target properties, ordinarily triggering a behavioural adjustment.

Looking at additional kinematic results from RB's reaches, it seems that her performance suffered due to deficits in both her visuomotor and perceptual networks. For example, she showed much longer reaches than controls in the closed-loop condition, yet her time-to-MGA, peak wrist velocity, and time-to-peak velocity were no different than controls. Taken together, these results illustrate the profile of a reach that is fairly normal, kinematically, at the start of the reach, but protracted closer to object contact. This suggests that RB was

taking more time than controls to carefully monitor her hand and finger position as she approached object contact. Such behaviour likely stems from the detection and attempted correction of reach errors during the movement rather than an anticipation of such inaccuracies prior to movement onset. When visual feedback of the reach is removed, RB exhibits a dramatic shift in her kinematic behaviour. Her movement times become even longer, the time it takes her to reach MGA and peak velocity are also protracted compared to controls, and her maximum wrist velocity greatly decreases – though not beyond the range of controls. These results indicate that RB's visuomotor system, which already struggled under normal viewing conditions, has a great deal of difficulty coping without visual feedback. It seems reasonable to conclude that these additional deficits stem from an already damaged visuomotor system now having to contend with incomplete or inaccurate information arriving from damaged perceptual systems elsewhere in the brain. RB's behaviour reflects this internal turmoil through slow, careful, protracted movements. Unfortunately, these careful movements could not overcome the destructive combination of damaged visuomotor and perceptual systems, as RB made inaccurate reach-to-grasps on 77.8% of trials in the immediate condition and 91.1% of trials in the delayed condition. In fact, her ability to guide her hand to a remembered target is so poor that RB missed the block's location completely on 73.3% of trials following a three second delay between object viewing and movement onset.

MTB. MTB demonstrated appropriate scaling behaviour during the closed-loop condition – a negative regression slope that was different from zero and no different from controls, with a reasonably high r-squared value of 0.444. However, once visual feed-back was removed for the immediate open-loop and delayed conditions, MTB's scaling was completely abolished. These results suggest that MTB's visuomotor system is intact insofar as her behaviour remains sensitive to object size when she has access to constant visual feedback. Once vision is

taken away, however, MTB's visuomotor system clearly lacks an accurate perceptual representation of the target object on which to base its calculations, resulting in a drastic change in performance between closed-loop and open-loop conditions.

Although MTB's scaling ability remains intact during normal, closed-loop grasping – implying proper visuomotor functioning – her other kinematic data tells a different story. MTB's movement duration was more than three times longer than controls, her peak velocity was consistently slower than controls, and it took her longer to achieve both MGA and peak velocity under free-viewing conditions. Therefore, while MTB was able to scale her grasps, she had to make slow and careful movements in order to produce this behaviour. Even with these extra precautions, MTB was forced to make grasp corrections on 17.8% of her reaches to objects in this condition. Taken together, these data imply that MTB's visuomotor system is not functioning normally compared to age-matched controls.

Like RB, MTB's already struggling visuomotor system coped no better when deprived of constant visual feedback of her actions. In open-loop conditions, MTB continued to produce longer movement durations, slower peak velocities, and longer times to MGA and peak velocity compared to controls. In addition, MTB showed the same counter-intuitive drop in overall MGA during open-loop grasping that we saw with RB, suggesting that MTB may be afflicted by similar disconnects between visuomotor, perceptual, and executive areas within her brain. MTB's inability to perform accurate reaches without visual feedback was best illustrated by the fact that only one of MTB's 90 grasps across both open-loop conditions was successful. More specifically, MTB was completely unable to guide her hand to the correct location of the target object on 98.9% of trials when her vision was occluded.

SS. SS showed significant scaling of his grip with respect to the size of the target object in the closed-loop condition, though the degree of scaling fell just outside of that of controls, indicating weaker scaling behaviour than normal. When vision was removed in the immediate open-loop condition, SS was still able to scale his grasps to the size of the object in a similar fashion to controls. However, this ability was lost once a delay was introduced between object viewing and movement onset. This result suggests that SS's perceptual system does not form a stable representation of the target object that persists for any substantial length of time. The fact that SS's scaling behaviour is maintained in the immediate open-loop condition but lost in the delayed condition reinforces the idea that the transition from online, visuomotor control to memory-based perceptual control is not immediate following visual occlusion (Himmelbach and Karnath, 2005). Despite losing the ability to scale his grasps in the delayed open-loop condition, SS maintained comparable reach kinematics to controls. Though he showed a fairly large increase in overall movement time in the delayed condition compared to the immediate condition, his time-to-MGA, peak velocity, time-to-peak velocity, and movement time all remained well within the normal control range.

Analysing the accuracy of SS's grasps adds further support to the previous observations. SS executed accurate grasps on 42 (93.3%) of his 45 grasps under visual guidance, as well as 36 (80.0%) of his 45 grasps in the immediate condition. While this performance is not perfect, it is not far off the performance of controls. As we might expect from SS's inability to scale properly after a delay, his reach accuracy also suffered in the delayed open-loop condition, where he made grip corrections on 28.9% of trials and missed the block completely on an additional 26.7% of trials. However, his performance was nowhere near as poor as RB and MTB, in that he made successful, accurate grasps on 44.4% of trials following a delay, while RB and MTB were successful on 8.9% and 0.0% of trials, respectively, under the same conditions.

Unlike RB and MTB, SS retains the ability to perform accurate grasps without visual feedback, although this ability is short-lived, as the introduction of a delay between object viewing and movement onset abolished his scaling behaviour. However, the presence of otherwise normal grasp kinematics in the delay condition, as well as his ability to execute accurate grasps on almost half of these trials, indicate that his visuomotor system is still able to retrieve some useful information from his perceptual system on which to program a grasp. Additionally, unlike RB and MTB, SS showed the expected increase in overall MGA following the removal of visual feedback, suggesting that his visuomotor system can still respond appropriately to the presence of inaccurate or incomplete target information by producing compensatory grasp strategies.

AP. Like MTB and SS, AP's ability to scale her grasps under visual guidance remains intact. Additionally, her time-to-MGA, peak velocity, and time-to-peak velocity were all within the normal range, although she exhibited significantly longer movement durations than controls. When visual feedback was removed, AP showed very similar behaviour to SS: She maintained her ability to accurately scale her grasps to the size of the object if allowed to reach immediately, but lost this ability when a three second delay was imposed. Her kinematic data for the open-loop conditions closely resembled those seen for closed-loop grasping: longer overall movement durations with normal time-to-MGA, peak velocity, and time-to-peak velocity.

AP showed some similarities and some differences to controls with respect to the pattern of changes in kinematics across conditions. Like controls and SS, AP showed an increase in overall MGA as task demands increased, moving from closed-loop to immediate open-loop grasping, and then from immediate to delayed grasping. She also showed an increase in overall

movement duration across the same conditions. However, AP did not show the same pattern of change in time-to-MGA, peak velocity, or time-to-peak velocity. Although, like controls, her time-to-MGA was longer in the immediate open-loop condition compared to closed-loop grasping, this pattern did not continue into the delayed condition, where her time-to-MGA actually reverted back to a value similar to the closed-loop condition. AP also showed no difference in peak velocity or time-to-peak velocity across conditions, while controls showed a decreasing velocity and increased time-to-peak velocity as task demands increased.

AP showed perfect grasping accuracy in the closed-loop condition, executing a successful grasp on all 45 of her reaches. Interestingly, despite the fact that she scaled her grasps in the immediate open-loop condition and failed to do so in delayed grasping, her accuracy between the two open-loop conditions was almost identical. AP was accurate in her grasping on only 15.6% and 17.8% of grasps in the immediate and delayed conditions, respectively, and missed the target object completely on 37.8% and 40.0% of trials over those same conditions. As such, it seems that AP's visuomotor system was able to retain or retrieve sufficiently accurate information regarding object size to program appropriate grip apertures in the immediate condition, but this information was lost following a brief delay. Conversely, information regarding the precise location of the target object seemed to elude AP in both open-loop conditions. It is possible that her perceptual abilities regarding shape and geometry are less impaired than those governing spatial localisation.

Conclusion. Study I revealed that all four PCA patients demonstrate varying degrees of visuomotor and perceptual malfunction. Specifically, RB shows a breakdown in visuomotor functioning on the most basic of reach-to-grasp tasks: picking up a simple, symmetrical object presented at her midline under free-viewing conditions. Though RB has no trouble initiating and

executing grasps to targets, she is unable to produce finger movements that accurately reflect the size of the object she is reaching for. Additionally, she shows significantly longer movement durations than controls. MTB, though able to scale her grasps to the size of target objects under closed-loop conditions, shows numerous kinematic abnormalities during prehension, including protracted movement durations and slower peak wrist velocities. SS and AP show relatively preserved visuomotor abilities under these basic testing conditions. However, AP still demonstrates unusually long movement durations, and there is evidence that SS's scaling behaviour is not as robust as controls. Together, these results suggest that damage to occipito-parietal areas of the brain resulting from progressive atrophy is affecting the basic visuomotor abilities of these patients.

Prior to this experiment, we hypothesised that PCA patients with dorsal steam deficits might experience an improvement in their grasping ability following visual occlusion if their impaired visuomotor systems were able to receive more accurate target information from intact perceptual representations stored in the temporal lobe. Unfortunately for our patients, this does not seem to be the case. RB showed no improvement in grasping behaviour in the open-loop conditions, while MTB's ability to scale her grasps under free-viewing conditions was lost the instant vision was occluded. SS and AP demonstrated a slight preservation of accurate visuomotor functioning for open-loop grasping, as they were able to scale their grip aperture to the size of the object in the immediate open-loop condition, but this behaviour disappeared for both patients when a three second delay was imposed. These results suggest that all four patients, in addition to their visuomotor dysfunction, also suffer from damage to temporal cortical areas that are ordinarily able to provide visuomotor systems with lasting perceptual representations of the environment.

Study II: Blake Shapes

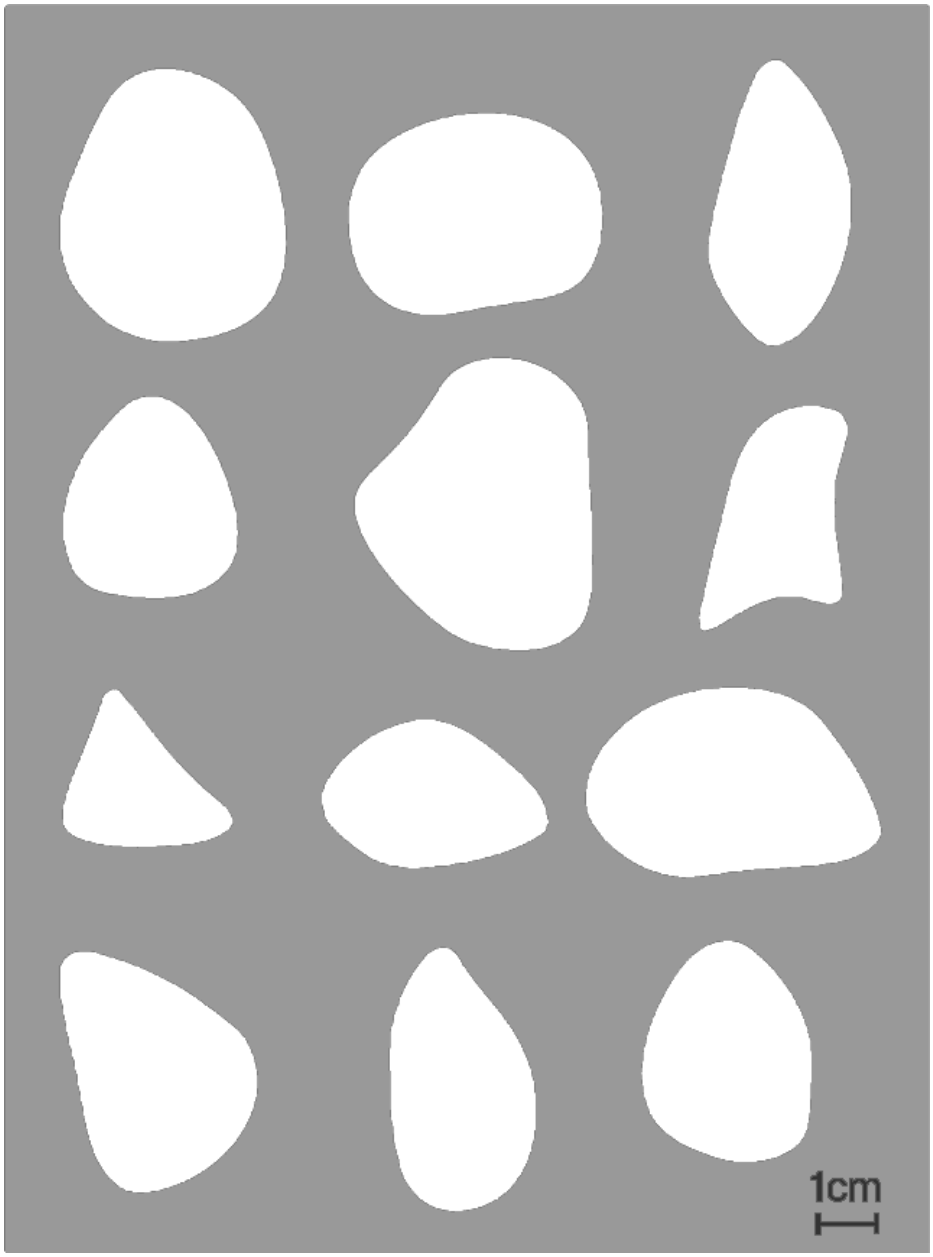
Background. An important aspect of precise and accurate grasping is the selection of stable grasp sites on an object. For smaller objects, like those used in this study, the most stable grasp sites are locations where the line of force application from the index finger to the thumb falls across the object's center-of-mass (CoM). As such, a line drawn from the index finger grasp location to the thumb grasp location should pass very close to an object's CoM. Previous experiments using the same stimuli presented here found that the majority of reaches made by control participants have grasp lines that fall within 2mm of an object's CoM (Goodale et al., 1994b; Marotta, McKeeff & Behrmann, 2003). Additionally, grasp lines usually fall along areas of the object that yield the most grasp stability: points of minimum or maximum object diameter, or points of maximum boundary curvature. These results provide one method of measuring proper grasping function; a subject executing accurate grasps should generate a majority of grasp lines that fall close to an object's CoM. By using this parameter to compare the grasps of PCA patients with those of control participants, we will gain a better understanding of how prehension is affected in PCA.

Accurate performance on the above task requires that visuomotor systems have access to complex shape-contour information as well as the ability to determine appropriate grasp sites. Evidence from visual agnosic patient, DF, suggests that occipito-parietal areas in the dorsal stream are indeed able to perform such operations; DF executes accurate grasps to irregular, asymmetric objects despite a complete inability to overtly distinguish object shape, size, or orientation (Goodale et al., 1994b; Goodale et al., 1991; Milner et al., 1991). Support for this conclusion comes from studies on so-called 'manipulation neurons' in the monkey parietal lobe, which not only control specific movements of the hand, wrist, and fingers, but also respond

preferentially to particular orientations and shapes of goal objects (Durand et al., 2007; Murata, Gallese, Luppino, Kaseda, & Sakata, 2000; Taira et al., 1990). Even though the discovery of visually-responsive, shape-sensitive cells in posterior parietal areas is a relatively new one, it has long been known that neurons in inferotemporal cortex respond to very specific object properties (Tanaka, Saito, Fukada, & Moriya, 1991) and are responsible for complex stimulus discrimination (Pribrama & Mishkin, 1955). Unlike the shape and contour information being fed to visuomotor systems, however, object information in ventral stream areas allows for explicit object identification and discrimination.

The current study exploits this difference in the output of the posterior parietal and inferotemporal cortices by presenting tasks that require participants to use shape-contour information, but that specifically target one or the other of the two visual processing streams. In the visuomotor task, participants were asked to reach out and pick up one of 12 asymmetrical, irregularly-shaped blocks called Blake shapes (see Figure 4). In the perceptual task, participants were asked to make a visual judgement as to whether two of these Blake shapes were the same or different from one another. This perceptual task was run twice under two different experimental conditions. First, in the tabletop condition, two physical blocks were presented simultaneously. Second, in the computer-based condition, two Blake shapes were presented consecutively on a computer screen. This second condition was used to help overcome the possibility that some patients with PCA may have performed poorly in the tabletop condition due to simultanagnosia, which may have impaired their ability to simultaneously evaluate two objects. The first perceptual condition is still useful for this study, however, as it uses more ecologically valid stimuli, and does not require the integrity of a subject's visual memory – something that may also be affected in PCA.

Figure 4. *The 12 Blake shapes used in Study II*



Methods. The visuomotor task and the tabletop portion of the perceptual task were performed concurrently using 12 pairs of asymmetrical, irregularly-shaped blocks known as 'Blake shapes'. These blocks are small, wooden objects cut to the same shape as templates used by Blake in the early 1990's to develop algorithms for the control of grasping using two-fingered robots (Blake, 1992). Previous studies have successfully used these objects for assessing grasp strategies and prehensile deficits in patient populations (Goodale et al., 1994b; Marotta et al., 2003). Our Blake shapes were 5mm thick and painted white. The two objects making up each pair were identical in every aspect that we could control: shape, size, colour, and texture. Blocks were presented on a dark-blue tablecloth in order to: provide adequate contrast between the white block and its background, maintain a consistent contrast difference between testing locations, and prevent ink stains on participants' dining room tables.

The tabletop portion of the perceptual task tested participants' abilities to determine whether two simultaneously presented blocks were identical or not. On each trial, two blocks were presented at the participant's midline: one block at a distance of 20cm from the edge of the table and the other at a distance of 30cm. Each shape was rotated to one of four orientations: 0, 90, 180, or 270 degrees from a predefined 'upright' condition for each shape. The participant's task was to visually inspect the pair of objects and verbally state whether they were "the same" or "different". There was no time limit; participants could take as long as they liked to view the objects and make a decision.

The visuomotor task required participants to reach out and pick up one object of each pair presented in the tabletop perceptual task – the other having first been removed – using their thumb and index finger in a precision grip. They wore synthetic 'finger cots' on each grasping finger and were instructed to blot their fingers with ink from an inkpad between each

trial. The ink left a physical marker of the grasp points on each block, which was then recorded by an experimenter.

A semi-randomised design was used to pair blocks together for a total of 96 trials for both the tabletop perceptual and visuomotor tasks. Each block was grasped eight times, and the two simultaneously presented objects were identical in 48 (50%) of the perceptual trails. Additionally, for half of the 48 trials in which the two objects were identical, the two blocks were also presented at the same orientation. In this way, a comparison could be made between the trials in which the orientation of the two identical blocks was the same and those in which it was different. This allowed us to determine whether difficulties in this task could be attributable to impaired mental rotation.

The computer-based condition of perceptual task was performed on a portable notebook computer. Graphic images of the Blake shapes were presented using E-Prime software, and consisted of white images on a black background in order to approximate the stimulus presentation conditions of the tabletop condition. The object pairings and object orientations were identical to those from the paradigm used for the tabletop condition, but the order of presentation was randomised. The main procedural difference between the two conditions, as mentioned above, was that pairs of objects were presented individually and consecutively in the computer-based condition, whereas they were presented simultaneously in the tabletop condition. Participants were seated directly in front of the computer screen, and were allowed to view each object for as long as they desired. Once participants had observed the first object in each pair, they were instructed to provide a verbal signal – by saying “ok” or “next” – at which point the experimenter cued the program to advance to the next object. When cued to advance, the program displayed a scrambled image for 300ms before proceeding

to the next image. This scrambled image was used to reduce the possibility of visual persistence following the removal of the first image. Once again, the subject could view the second object for as long as they liked before making a same/different judgement. The participants were instructed to provide a verbal response once a decision had been made, and the experimenter recorded the response before cueing the next trial.

Analysis. For the tabletop condition, a score – percent correct – was generated based on the number of correct responses out of the total number of trials. A 95% confidence interval was then generated based on the scores of all control participants. Patients' scores were compared to those of controls – their performance on the perceptual tasks being considered 'normal' if they fell within the 95% confidence interval. For controls, a paired-samples *t*-test was performed to compare their performance on the 24 trials in which the two presented objects were the same shape at the same orientation versus the 24 trials in which the two objects were the same shape at different orientations. A significant difference in the accuracy scores between these conditions would indicate that rotating the targets reduced the ability of controls to accurately identify similarly shaped objects. To see if patients suffered a similar loss in accuracy, a 95% confidence interval was created for control data based on the average 'difference score' between the two orientation conditions. This difference score was calculated by subtracting each participant's accuracy score on trials in which the objects were the same shape but presented at different orientations, from their accuracy score on trials in which the objects were the same shape and the same orientation. Patients' difference scores were considered abnormal if they fell outside the 95% confidence interval for control data. Analysis for the computer-based condition was identical to that presented above for the tabletop condition.

In order determine whether each patient's ability to perform this task was affected by more than just a change in difficulty between tasks, a second difference score was calculated for each participant. This difference score represented the participant's score in the tabletop condition subtracted from their score in the computer-based condition. As such, a negative difference score represents a poorer performance on the computer-based task compared to the tabletop task. A 95% confidence interval was then created surrounding the average difference score for all controls. Patients' difference scores were compared to this confidence interval to determine if a patient's score changed between tasks in a manner different from controls.

Using image-processing software and a custom-made Matlab program, templates of the Blake shapes were generated and their exact CoM was calculated. Images of these templates were printed at a one-to-one size ratio to that of the true objects. As the participants were run on the grasping task, the grasp locations for each trial were recorded on the corresponding block template. A 'grasp line' was generated for each trial by drawing a line between the index finger and thumb grasp points. A 'distance to CoM' variable was calculated by measuring the shortest perpendicular distance from each grasp line to the object's CoM. A percentage score was calculated for each participant by comparing the number of grasp lines that fell within a 5mm-diameter region of interest (ROI) surrounding the CoM to the total number of grasps. This size of ROI was chosen to closely approximate that which has been used in previous grasping studies that employed the same target stimuli (e.g. Marotta et al., 2003). The performance of the four patients was compared with that of controls by constructing a 95% confidence interval for the pooled control data. An additional comparison was made by calculating the average 'distance to CoM' – the total distance of all grasps divided by the total number of grasps. Again, a 95% confidence interval was created using the control data, and patient results were compared to this interval. Results were expected to be very similar for these two comparisons,

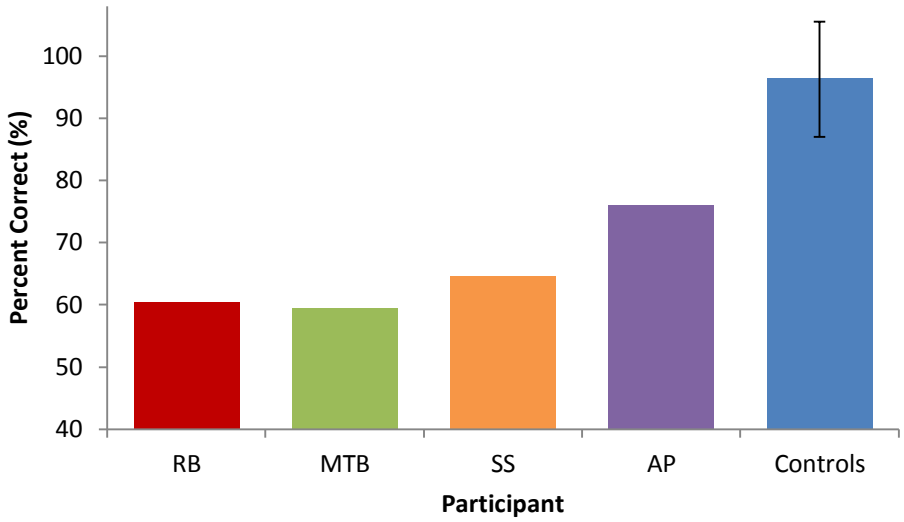
since participants who had fewer grasps falling within the 5mm ROI were likely to have a larger average grasp distance.

Results.

When performing the tabletop portion of the perceptual task, control participants had very little problem identifying whether the two simultaneously presented objects had the same or different shape, scoring 96.3% correct. Conversely, all four patients struggled with this task, scoring significantly worse than controls ($p<0.05$; see Figure 5.a). Controls found the computer-based task to be more challenging, as shown by an overall drop in correct responses ($t(4)=5.636$, $p=0.006$). Despite the increased task difficulty, controls were still able to perform this task with a high level of accuracy, averaging 87.3% correct (see Figure 5.b). Though RB, MTB, and SS once again scored significantly worse than controls ($p<0.05$), AP's score actually improved compared to the tabletop condition. This improvement, coupled with the reduction in controls' average score, resulted in AP's score falling within the interval of normality as provided by the control data ($p>0.05$).

Breaking down the scores from the tabletop condition to consider the orientation of the blocks, we see that orientation had no impact of the ability of controls to judge whether or not the shapes of two objects were the same or different ($t(6)=-0.354$, $p=0.736$; see Figure 6.a). Similarly, though MTB showed a very slight decrease in score when the blocks were orientated differently, this change in accuracy was no different than controls ($p>0.05$; see Figure 6.b). Conversely, RB, SS, and AP's precision dropped to roughly chance levels when blocks were presented at different orientations, a marked decrease in accuracy compared to controls ($p<0.05$). Though RB's performance had already been poor on the same orientation condition,

Figure 5.a. *Scores on the tabletop same/different task*



Note. Error bars on the control data represent a 95% confidence interval.

Figure 5.b. *Scores on the computer-based same/different task*

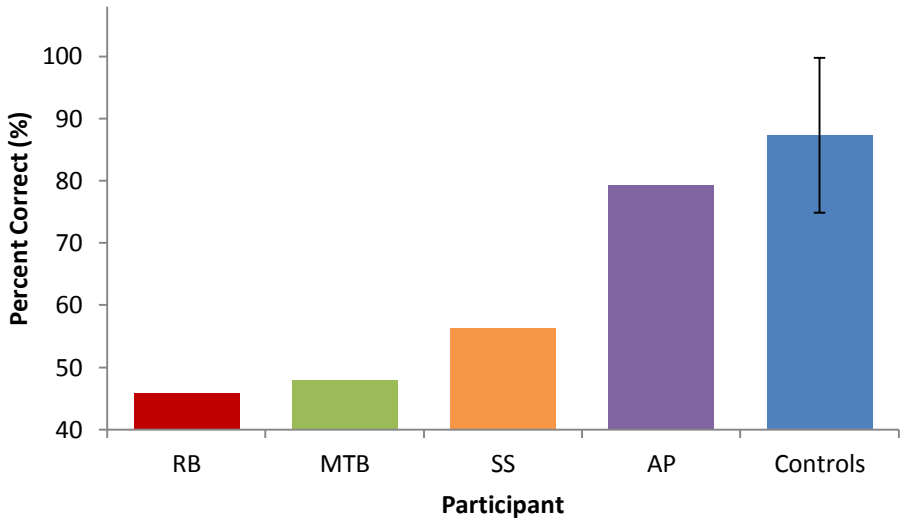
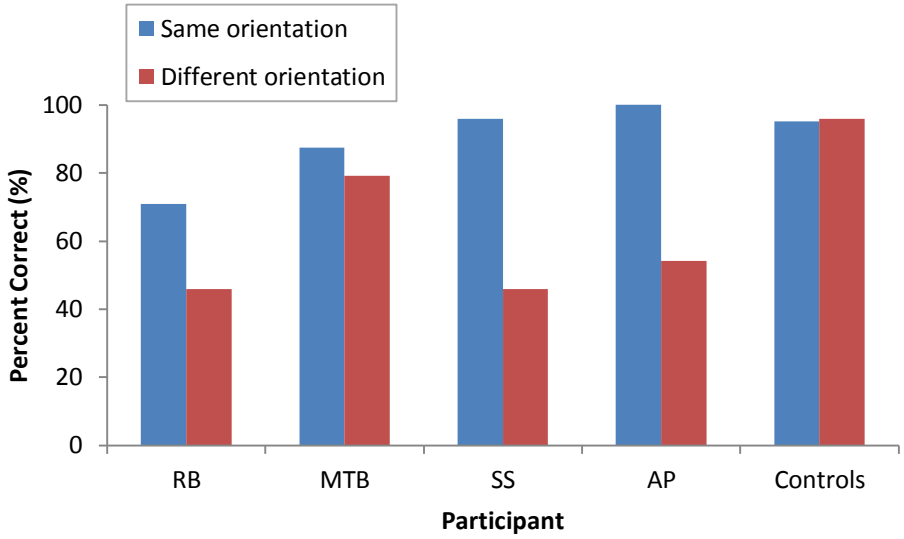
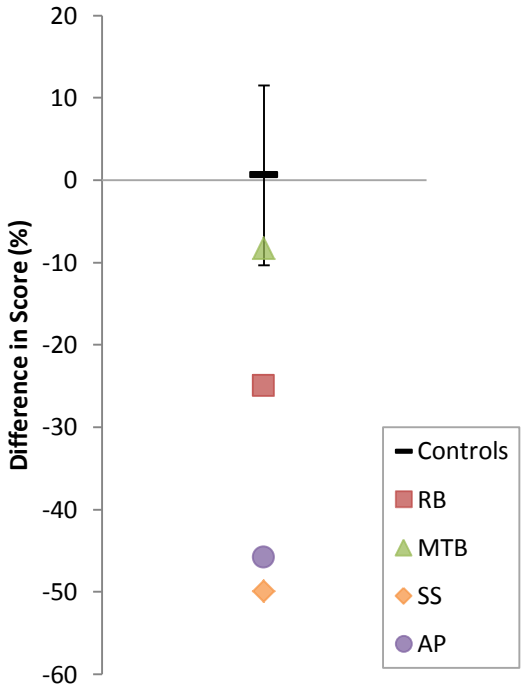


Figure 6.a. *Effect of block orientation on performance: tabletop task*



Note. Data set includes only those trials on which the two blocks were the same shape.

Figure 6.b. *Difference in performance between orientation conditions: tabletop task*

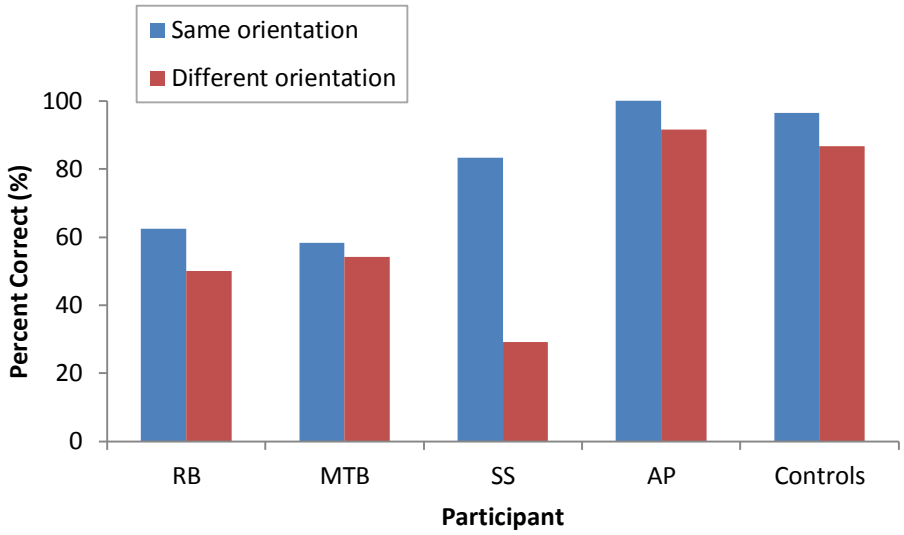


Note. Error bars on the control data represent a 95% confidence interval.

this drop in accuracy was dramatic for SS and AP, who both scored over 95% correct when objects were at the same orientation. As such, it seems that RB, SS, and AP all show impairments in their ability to complete tasks requiring mental rotation. When this same analysis was performed on the scores from the computer-based task, we saw slightly different results (see Figure 7.a). Once again, controls performed equally well when objects were presented at different orientations compared to when they were at the same orientation ($t(5)=1.435$, $p=0.211$). This time, however, SS was the only patient who showed a significantly greater drop in accuracy than controls when the identical objects was presented at different orientations ($p<0.05$; see Figure 7.b). It should be noted, though, that RB and MTB's accuracy was relatively close to chance levels when the objects were at the same orientation, so it's possible that the only reason we saw no drop in their performance for differently oriented objects is that their performance couldn't get much worse to begin with.

Looking at the confidence interval of difference scores representing the change in accuracy between the tabletop and computer-based tasks, we see that AP was the only patient whose change in performance was different from that of controls (see Figure 8). RB, MTB, and SS all show similar decreases in accuracy compared to controls, representative of the increased difficulty of the computer-based task ($p>0.05$). AP, however, showed an *increased* score on the computer-based task – a change that was significantly different from controls ($p<0.05$). In other words, even though AP's score increased only slightly between tasks, this increase was significant since her score was actually expected to *decrease* due to the increased difficulty of the task.

Figure 7.a. *Effect of block orientation on performance: computer task*



Note. Data set includes only those trials on which the two blocks were the same shape.

Figure 7.b. *Difference in performance between orientation conditions: computer task*

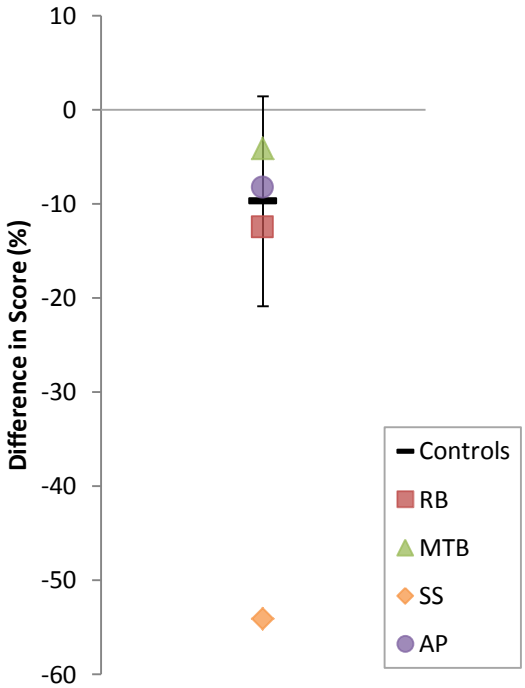
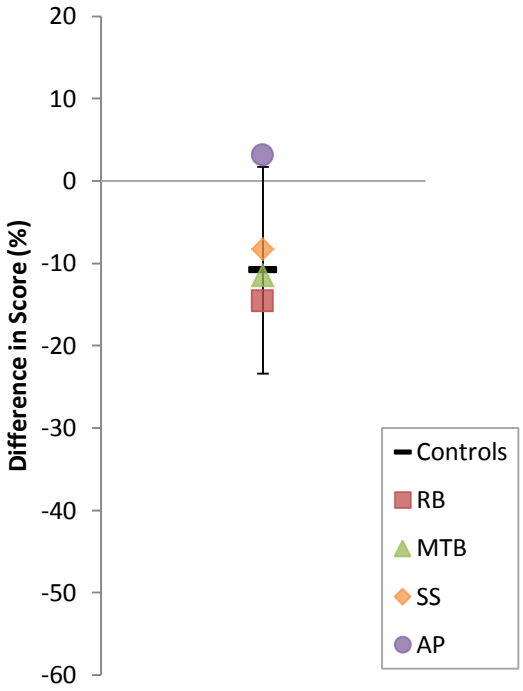


Figure 8. *Difference in performance between tabletop and computer conditions*



When asked to reach out and pick up the same blocks used in the perceptual task, 52% of grasps made by controls fell within the 5mm ROI surrounding the objects' CoM (see Figures 9 and 10.a). A similar proportion of the grasps made by RB and SS fell within the same region ($p>0.05$). Conversely, MTB and AP's grasps were much less accurate, with fewer than 35% of their grasps falling within the ROI ($p<0.05$). A similar pattern of behaviour was revealed when looking at the average distance to CoM: RB and SS showed very similar average grasp distances compared to controls ($p>0.05$; see Figure 10.b), while MTB and AP made grasps that fell significantly further from the CoM ($p<0.05$).

Discussion.

RB. As might be expected based on the difficulties RB showed on tests of basic visual perception, as well as her poor performance during the open-loop conditions in Study I, RB showed a distinct inability to compare and contrast objects based on their shape. This deficit was apparent in both the tabletop condition – in which two objects were presented simultaneously, and the computer-based condition – in which two objects were presented sequentially. Under both conditions, RB's ability to assess the difference between the two blocks fell at around chance level, though she performed slightly better in the tabletop condition. The similarity of RB's performance across the two experimental conditions suggests that her inability to perform this task is not purely a result of an inability to attend to multiple objects at the same time – due to simultanagnosia, or a deficit in visual memory. Instead, it seems that RB suffers from a genuine inability to accurately process the shape of an object. However, we cannot rule out the possibility that simultanagnosia is actually the underlying cause of this shape-perception

Figure 9. *Distribution of grasp distances from CoM in Study II*

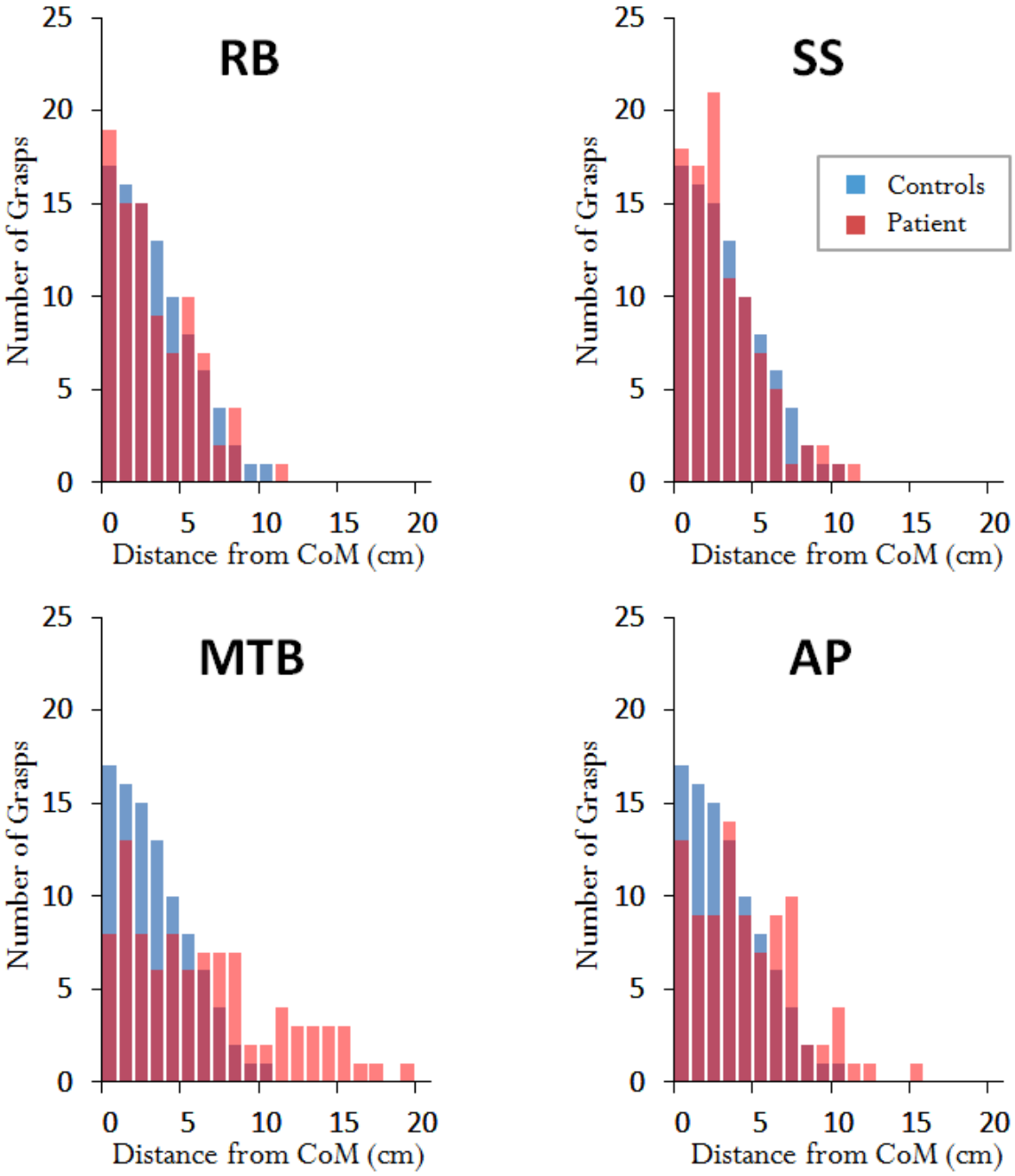


Figure 10.a. *Grasp stability in Study II: Number of grasps within 5mm ROI*

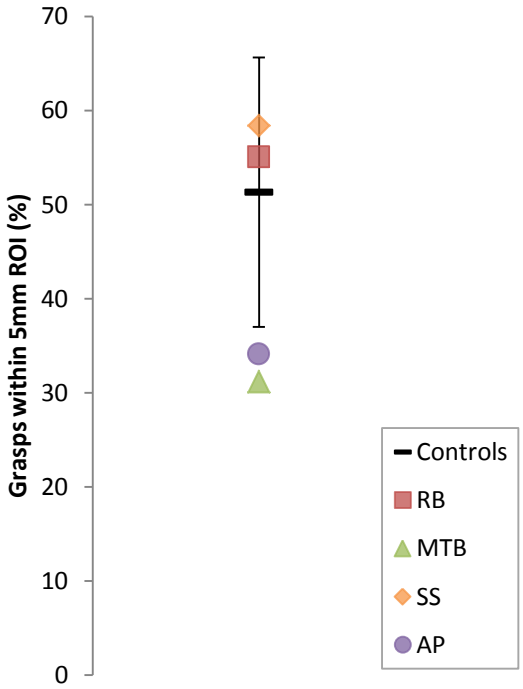
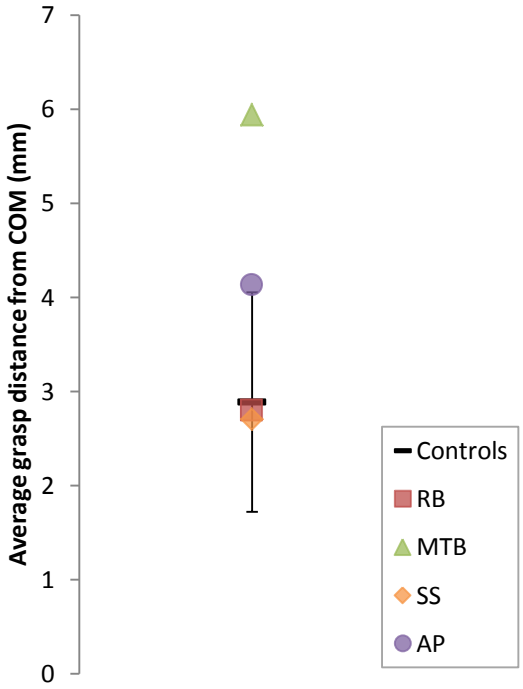


Figure 10.b. *Grasp stability in Study II: Average grasp distance from CoM*



deficit. For example, if RB's simultanagnosia is severe enough that she can only attend to one specific element of an individual shape, then this would clearly affect her ability to analyse the overall contour of an object.

RB's results from the visuomotor component of Study II appear to be in contrast from those seen in Study I. RB showed no impairment in guiding her fingers to stable grasp sites on the unusually-shaped, asymmetrical Blake Shapes, but was unable to accurately scale her grip to the size of the simple, symmetrical Efron Blocks used in Study I. These results suggest that RB's visuomotor system, despite showing an obvious breakdown in some situations, is still able to perform other tasks fairly normally. It may be that atrophy in RB's parietal cortex has damaged very specific functions within her visuomotor systems while sparing others. Given the progressive nature of PCA, one might expect that as the disorder progresses, RB's visuomotor deficits will become more extensive as additional facets of her visuomotor system are eroded. This result is also fascinating as it speaks to the impressive ability of the visuomotor system to independently analyse the shape of an object with which it wishes to interact. RB demonstrated a complete inability to use information regarding the shape of target objects when asked to compare them perceptually, yet her accuracy in selecting stable grasp sites on these same objects reveals that her visuomotor system has retained its ability to analyse the contours of an object. This observed dissociation in behaviour supports the idea that visuomotor systems can act completely independently of their perceptual counterparts when required to calculate the shape, orientation, and location of objects in our environment.

MTB. MTB's performance across Studies I & II offers an interesting contrast to that of RB. While RB was able to select stable grasp sites on the Blake Shapes in Study II and showed no evidence of grip scaling in Study I, MTB was the opposite. MTB showed normal scaling behaviour

for the Efron Blocks, but her selection of grasp sites for the asymmetrical Blake Shapes was poor. This lack of precision was reflected by a lower percentage of grasps falling close to the objects' CoM, and a larger average grasp distance from CoM. Like RB, this difference in visuomotor ability depending on the task suggests that atrophy affecting MTB's parietal cortex may be patchy and incomplete – damaging certain key functions while sparing others.

Like RB, MTB's performance on the perceptual same/different tasks reflects the difficulties she showed with open-loop grasping in Study I. In both the tabletop and computer-based conditions, MTB scored at chance level – close to 50% accuracy. As we concluded with RB, this result suggests a deficit in shape processing at the perceptual level, which is presumably controlled by the ventral stream. Once again, however, dorsal simultanagnosia cannot be ruled out as the possible underlying cause of this dysfunction.

SS. SS was able to accurately select stable grasp sites on the Blake Shapes and guide his fingers to these positions. However, like RB and MTB, SS exhibited a great amount of difficulty making same/different judgements regarding the Blake shapes in both the tabletop and computer-based conditions. These results parallel those seen in Study I, where SS showed appropriate scaling behavior in the closed-loop condition, but lost this ability following a three second delay. Together, these data suggest that the damage to SS' perceptual systems is more severe and extensive than the damage to his visuomotor system.

AP. AP's accuracy on the same/different task for the tabletop condition was noticeably better than that of the other three patients, but her performance was still impaired in relation to controls. However, when given the same task in the computer-based condition, AP's performance was normal. In fact, AP was the only participant whose accuracy was higher in the computer-based condition compared to the tabletop condition. What could be driving this

behaviour? The most parsimonious explanation is that AP's simultanagnosia prevented her from effectively switching her attention between the two objects on the table in order to compare them. When presented with the objects individually on the computer screen, however, no such attentional shifting was required. Instead, AP was able to form a perceptual representation of the single object before a new object was presented, at which point she could compare the current image to her perceptual representation of the previous object.

AP executed grasps to less stable positions on the Blake Shapes than controls, as shown by a reduced percentage of grasps falling close to the CoM and an increased average grasp distance from CoM. Like MTB, AP's impaired visuomotor abilities on this task, coupled with her relatively preserved grip scaling in Study I, suggest that damage to her parietal cortex is not systematic. Instead, certain visuomotor functions seem to have been spared by the progressive atrophy, while others have already been irreparably damaged.

Conclusion. The design of this task provided an interesting comparison between the functions of the perceptual and visuomotor systems. Both the visuomotor and perceptual tasks required that participants make a complete shape-contour analysis of the target objects. In the grasping task, participants had to consider the entire contour of each shape in order to properly select stable grasp sites. For most of us, this endeavor is performed accurately, quickly, and efficiently countless times each day. Such functioning is thought to be carried out by fast visuomotor systems in the parietal lobe, independent of input from perceptual systems. The same/different task also requires that a shape analysis of each object be performed, but this procedure is more effortful and is the domain of perceptual systems in inferotemporal cortex. RB, MTB, and SS all showed a dramatic inability to accurately determine whether two objects were the same or different from one another. This deficit was apparent whether the two shapes

were presented simultaneously or individually. AP, on the other hand, demonstrated difficulty with this task when both objects were presented at the same time, but not when the objects were shown sequentially. This behaviour suggests that AP's ability to compare the two shapes in the tabletop task was marred by a specific inability to attend to multiple objects simultaneously. The grasping portion of this study revealed that RB and SS had no difficulty in selecting and guiding their fingers to stable grasp sites on irregularly shaped objects, while MTB and AP clearly struggled with this task. In addition to contributing valuable knowledge of the effects of PCA on perceptual and visuomotor functioning, these observations also add credence to theories which state that visuomotor and perceptual systems can perform similar processes – albeit to achieve different results – independently, yet equally effectively.

Study III: Peripheral Grasping

Background. Integral to Milner and Goodale's two-stream theory of visual processing is behavioural evidence from patients with selective lesions in the parietal lobe. These patients often exhibit an inability to execute accurate visually-guided goal-directed reaching and grasping movements despite being free of visual acuity or visual field deficits and having intact primary sensory and motor systems (Karnath & Perenin, 2005). Termed 'optic ataxia', this disorder is seen in patients with damage to cortical areas surrounding the intraparietal sulcus (IPS). Individuals with optic ataxia often show deficits in both the proximal and distal components of grasping movements, including: prolonged movement times (Binkofski et al., 1998), inaccurate reaches to visual targets (Cavina-Pratesi, Ietswaart, Humphreys, Lestou & Milner, 2010), a disturbance or complete lack of in-flight hand shaping for object size (Jakobson et al., 1991), an inability to make fast corrective movements while reaching to perturbed stimuli (Gréa et al., 2002), abolished implicit obstacle avoidance (Schindler et al., 2004), and inappropriate wrist-

orientation for the task demands (Perenin & Vighetto, 1988). Optic ataxia can result from unilateral parietal damage to either hemisphere, with the resulting visuomotor problems primarily affecting the contralesional hand and the contralesional visual hemifield. Alternatively, optic ataxia can result from bilateral damage, with both hands and both hemifields being affected. Different patterns of hand and hemifield disruptions have been observed between patients, which has strengthened the argument that optic ataxia is neither a disorder of motor impairment nor of visual-field defect. For example, patients who show visuomotor deficits with one hand in one hemifield, but not with that same hand in the opposite hemifield, demonstrate that motor impairment is not the underlying issue. Meanwhile, patients who exhibit visuomotor deficits with one hand in one hemifield, but not the other hand in that same hemifield, demonstrate that visual-field defect is not the underlying issue. Despite this variation in symptom presentation, it is most common that patients with optic ataxic demonstrate visuomotor deficits with both hands in the contralesional hemifield (Karnath & Perenin, 2005). Importantly though, even with bilateral lesions, individuals with optic ataxia usually exhibit reaching and grasping deficits only when performing tasks in their peripheral visual fields. In other words, when allowed to orient their eyes towards a target, patients' visuomotor performances are often no different from those of controls (Himmelbach, Karnath, Perenin, Franz, & Stockmeier 2006). Although this pattern of behaviour is the most common consequence of optic ataxia (Buxbaum & Coslett, 1997), it is not always the case; patients with optic ataxia have been known to demonstrate deficits in reaching and grasping under foveal guidance (Binkofski et al., 1998; Perenin & Vighetto, 1988). These observations raise an important question for the current study: do patients with PCA demonstrate differences in visuomotor functioning depending on the hand being used and the location of action in the visual field?

It has been documented that patients who show reaching mislocalisations due to damage to posterior parietal brain areas – both from acute injuries as well as degenerative disorders – often demonstrate a reaching bias towards the point of fixation when confronted with targets located in their visual peripheries (Carey, Coleman, & Della Sala, 1997; Jackson, Newport, Mort, & Husain, 2005; Ratcliff & Davies-Jones, 1972). Meanwhile, there is evidence that normal controls show the opposite behaviour – a horizontal 'overshoot' away from the point of fixation (Henriques & Crawford, 2000; Henriques, Klier, Smith, Lowry, & Crawford, 1998; Khan, Lawrence, Franks, & Buckolz, 2004). Given the location of cortical atrophy in our patient group, we sought to determine whether PCA patients exhibit a similar pathological reaching bias during reaches to peripheral targets.

Methods. A similar set-up to the previous two studies was employed for the peripheral grasping experiment. Participants were seated directly in front of a dark table and asked to reach out and pick up objects presented to them on the tabletop. For this task, participants were required to maintain fixation for the entirety of each trial at a central fixation point located on the tabletop at their midline. The fixation point was positioned 30cm from the edge of the table. An experimenter seated opposite the subject ensured that fixations were maintained at the central fixation spot. If participants did not maintain fixation with the central point for the entirety of the trial, then that data was not used and the trial was repeated at a later time. Each trial consisted of one of the three target blocks used in Study I – block A, block C, and block E – being presented, one at-a-time, at one of three possible locations. The first object-location was the fixation point itself, thereby providing a condition of grasping under central vision. The remaining two object-locations were 12cm to the left and right of the fixation point, which roughly corresponded to a 22° viewing-angle from the subject's location. When objects were presented at the two peripheral locations, their more proximal edges were positioned at the

12cm distance, thereby ensuring that no part of any object fell closer than 12cm to the subject's point-of-fixation, regardless of their size.

As with the previous two studies, participants were provided with a 'start button' – a raised landmark 7cm from the edge of the table – to which they were instructed to return their hand after each grasp. Between all trials, participants kept their index finger and thumb together and resting on the start button, with their remaining fingers tucked comfortably against their palm. Participants were instructed to close their eyes until a verbal prompt was given to open and commence fixation. Once fixation had been achieved, the experimenter gave a second verbal prompt allowing the participant to execute a reach to the target object. Some patients found it difficult to suppress the urge to glance at the target object before fixating at the central point. In these cases, a black cloth was used to cover the object until fixation had been achieved, thus preventing the patient from receiving target information prior to the reach. Participants were required to execute a precision grasp – using only their index finger and thumb in opposition – to each object, grasping the blocks across their vertical axis. Each of the three target-blocks was presented 5 times at each location, and the entire procedure was repeated for each hand. Thus, participants made 45 grasps with each hand, for a total of 90 trials per testing session.

Position and velocity recordings were made using a portable Motion Monitor system (Innovative sports technology; Chicago) attached to magnetic sensors. Individual sensors were attached to the index finger, thumb, and wrist. This setup allowed for the measurement of grasp dynamics, including MGA, wrist velocity, and reach trajectory.

Analysis. Finger position data from the magnetic sensors was captured by Motion Monitor software. As in Study I, this software calculated grip aperture and exported the value of

MGA for each grasp. For each patient, a separate regression analysis was run on MGAs for each hand and for each location. This analysis was used to reveal whether patients' grip apertures scaled in relation to the size of the block – as shown by a regression slope significantly different from zero – at each location.

As in Study I, four additional kinematic variables were measured and analysed for this study: time-to-MGA, peak velocity, time-to-peak velocity, and movement duration. 'Time-to-MGA' was the time it took for MGA to be achieved following movement onset. 'Peak velocity' was the maximum forward velocity reached by the wrist throughout the course of the reach-to-grasp movement. 'Time-to-peak velocity', like time-to-MGA, was the time between movement onset and peak wrist velocity. 'Movement duration' was defined as the total time taken to complete the grasp. The timing of the reach began at 'movement onset' – the time at which forward wrist velocity exceeds 0.05 m/s, and object contact – signified by the end of the trial. In order to compare the behaviour of patients to that of controls, a 95% confidence interval was generated surrounding the mean value for each kinematic variable, separated by hand and target-location. Individual patient data were then plotted against these confidence intervals to determine if patients were performing in a different manner compared to controls. A within-subjects *t*-test was run to ascertain whether there were overall differences in kinematics between participants' right and left hands. Additionally, single-subject ANOVAs were run to test for significant differences across target-locations for each kinematic variable. Post hoc analysis using Tukey's Honestly Significant Difference (Tukey's HSD) test was used to determine the exact 'location' of any main effects. Using these analyses, we are able to see how patients' grasping behaviour differed between their hands as well as between grasps to different hemifields. We were also able to compare this behaviour to that of controls to determine the situations in which their prehension would be considered abnormal.

Custom-written analysis software was assembled using Python in order to study the path of the hand as it moved from the start position to the target. All positional information was taken from the magnetic sensor attached to each participant's wrist. The start position for each trial was defined as the location of the wrist at 'movement onset', while the end position was the location of the wrist at the end of the trial. For each trial, an idealised, straight-line path was calculated between the start and end positions of the wrist. The deviation of the actual reach from this idealised path was then calculated by measuring the distance between the two paths at 30 equally-spaced points along the idealised line. This method enabled us to find the average path taken by a particular participant – or group of participants – within a particular condition by averaging the distance between the actual and idealised paths at each of the 30 points across multiple trials. By combining the behaviour of all control participants, we were able to generate the 'normal' path taken by controls to targets located at each position. The main variables of interest were the maximum leftward and rightward deviation of the reach from the idealised path for each trial. 95% confidence intervals were generated for control data for each block location. These intervals allowed us to see whether reaches made by controls differed from the idealised, straight-line paths, as well as whether the reaches made by each patient differed significantly from the paths taken by controls. To investigate the prominence of magnetic misreaching in movements directed toward peripheral targets, we recorded the number of trials in which the index finger passed through a 3cm-radius region of interest (ROI) around the fixation point. The size of the ROI was determined prior to analysis based on the dimensions of the experimental setup. Three centimeters was deemed to be large enough to catch any reaches directed specifically towards the fixation point, but small enough to avoid counting the vast majority of 'normal' reaches. For those trials on which reach paths passed through the ROI, a

qualitative kinematic analysis of the trajectory was performed to observe any differences in behaviour on these trials.

Results.

Controls. The control group showed significant scaling behaviour at midline with both their right and lefts hands ($p<0.05$). This scaling behaviour was preserved when participants were forced to reach for objects located in their visual periphery, where controls had no problem scaling their grasps to the size of the object with their right and lefts hands for both ipsilateral and contralateral targets ($p<0.05$; see Tables 3 and 4). Controls also showed no difference in overall MGA, time to MGA, time to peak velocity, or movement time between their right and left hands ($p>0.05$), but their peak velocity was slightly slower with their non-dominant left hands (0.66m/s) compared to their right (0.72m/s; $t(536)=4.811$, $p<0.05$). For reaches made with their right hands, movement time ($F(268)=5.518$, $p<0.05$), overall MGA ($F(267)=14.892$, $p<0.05$), and time to reach peak velocity ($F(268)=7.738$, $p<0.05$) all differed depending on the location of the target object (see Figure 11). Post hoc analysis revealed that these effects were driven by differences in the kinematics for contralateral reaches compared to the other two locations. Specifically, reaches to objects on the left produced longer movement times, larger overall MGAs, and longer times to peak velocity. We saw a similar pattern of behaviour for reaches made with the left hand, where there were differences in movement duration ($F(268)=11.083$, $p<0.05$), time to peak velocity ($F(268)=20.201$, $p<0.05$), time to MGA ($F(268)=9.897$, $p<0.05$), and peak velocity ($F(268)=3.875$, $p<0.05$) between object locations (see Figure 12). Post hoc analysis revealed that controls showed longer movement durations, longer times to reach peak velocity, and longer times to reach MGA for contralateral reaches compared

Table 3.a. *Regression values for midline grasping with the dominant hand*

	Slope	R^2	p-value
RB	-.130	.010	.729
SS	-.208	.054	.405
AP	-.418	.617	.001
Control I (BH)	-1.005	.888	<0.001
Control II (GI)	-.570	.628	<0.001
Control III (II)	-.682	.875	<0.001
Control IV (KS)	-.791	.529	0.002
Control V (TS)	-.824	.835	<0.001
Control VI (VD)	-.915	.913	<0.001

Table 3.b. *Regression values for ipsilateral grasping with the dominant hand*

	Slope	R^2	p-value
RB	-.291	.231	.096
SS	-.148	.019	.624
AP	-.123	.090	.276
Control I (BH)	-.633	.573	.001
Control II (GI)	-.353	.519	.004
Control III (II)	-.382	.489	.004
Control IV (KS)	-1.001	.706	<0.001
Control V (TS)	-.460	.528	.002
Control VI (VD)	-.427	.375	.015

Table 3.c. *Regression values for contralateral grasping with the dominant hand*

	Slope	R^2	p-value
RB	-.115	.022	.594
SS	-.169	.025	.575
AP	.018	.001	.930
Control I (BH)	-.435	.373	.016
Control II (GI)	-.268	.231	.070
Control III (II)	-.209	.120	.207
Control IV (KS)	-.958	.686	<0.001
Control V (TS)	-.577	.532	.003
Control VI (VD)	-.321	.330	.025

Table 4.a. *Regression values for midline grasping with the non-dominant hand*

	Slope	R^2	p-value
RB	-.195	.113	.222
SS	-.534	.370	.016
AP	-.147	.033	.519
Control I (BH)	-.940	.908	<0.001
Control II (GI)	-.652	.675	<0.001
Control III (II)	-.620	.792	<0.001
Control IV (KS)	-.711	.571	.001
Control V (TS)	-1.046	.944	<0.001
Control VI (VD)	-.690	.723	<0.001

Table 4.b. *Regression values for ipsilateral grasping with the non-dominant hand*

	Slope	R^2	p-value
RB	.029	.002	.876
SS	-.714	.273	.046
AP	-.127	.015	.665
Control I (BH)	-.528	.649	<0.001
Control II (GI)	-.231	.116	.214
Control III (II)	-.184	.261	.052
Control IV (KS)	-.602	.382	.014
Control V (TS)	-.598	.680	<0.001
Control VI (VD)	-.281	.221	.077

Table 4.c. *Regression values for contralateral grasping with the non-dominant hand*

	Slope	R^2	p-value
RB	-.597	.619	<0.001
SS	-.621	.194	.100
AP	-.136	.012	.692
Control I (BH)	-.186	.336	.023
Control II (GI)	-.362	.171	.141
Control III (II)	-.499	.262	.051
Control IV (KS)	-.620	.490	.004
Control V (TS)	-.410	.373	.016
Control VI (VD)	-.510	.620	<0.001

Figure 11.a. *Maximum Grip Aperture for reaches in Study III: dominant hand*

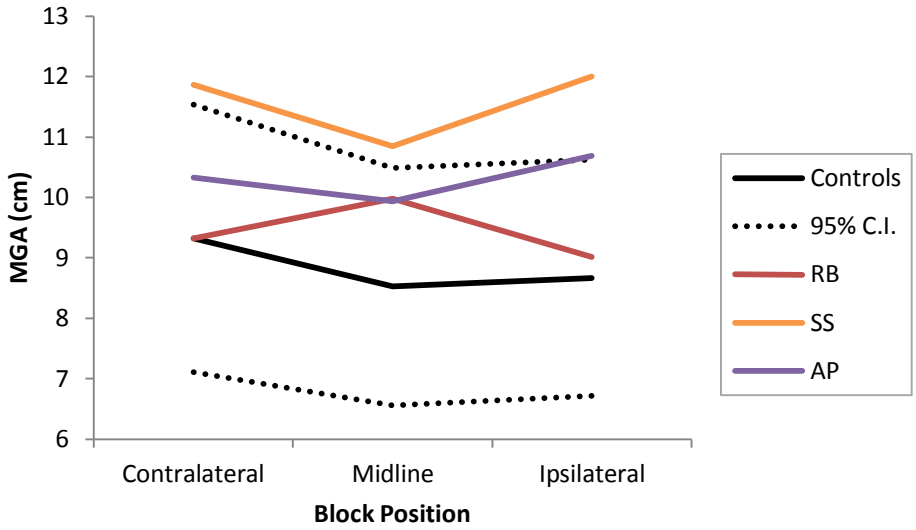


Figure 11.b. *Time to MGA for reaches in Study III: dominant hand*

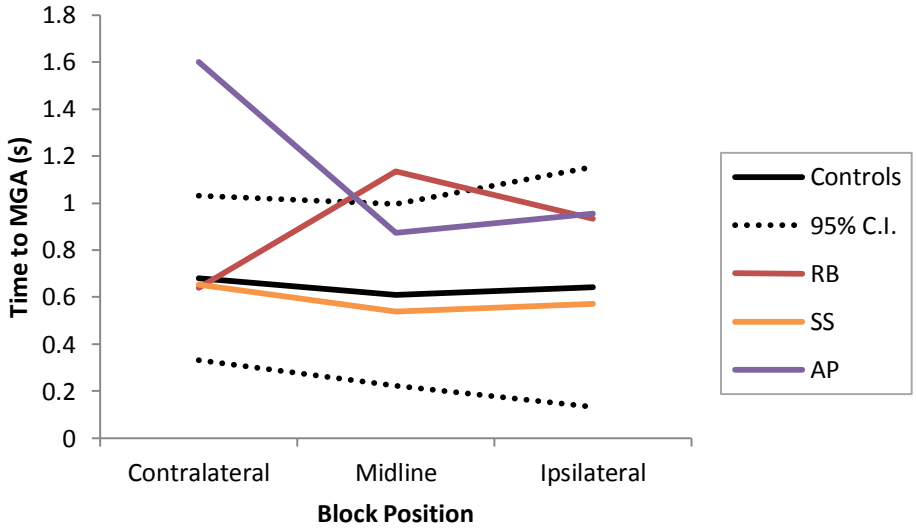


Figure 11.c. *Peak Velocity for reaches in Study III: dominant hand*

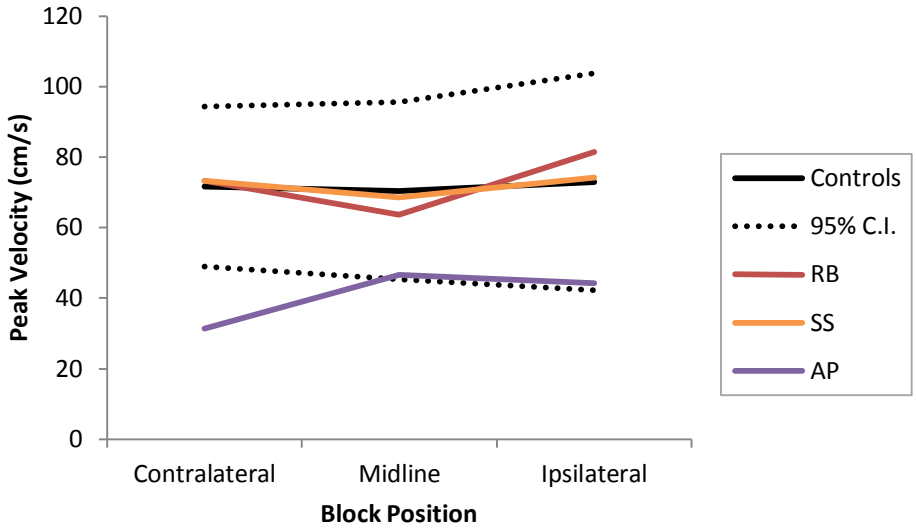


Figure 11.d. *Time to Peak Velocity for reaches Study III: dominant hand*

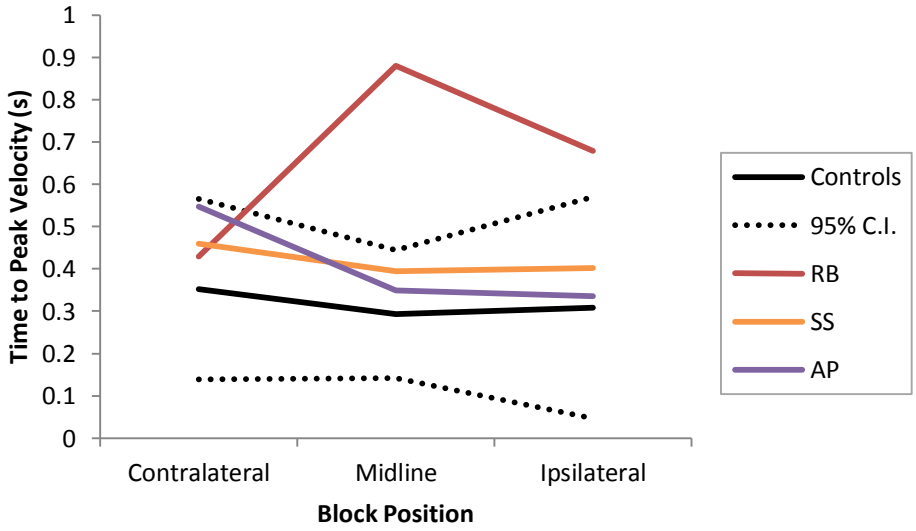


Figure 11.e. *Movement Duration for reaches in Study III: dominant hand*

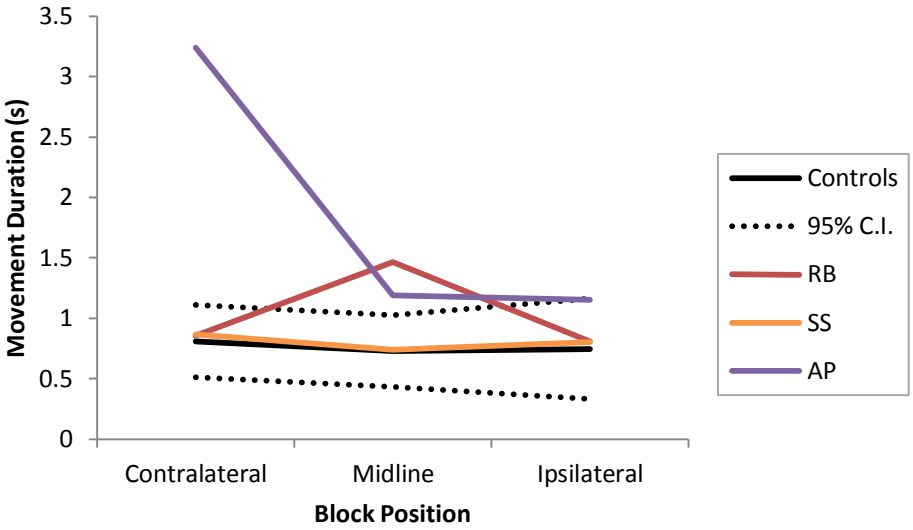


Figure 12.a. *Maximum Grip Aperture for reaches in Study III: non-dominant hand*

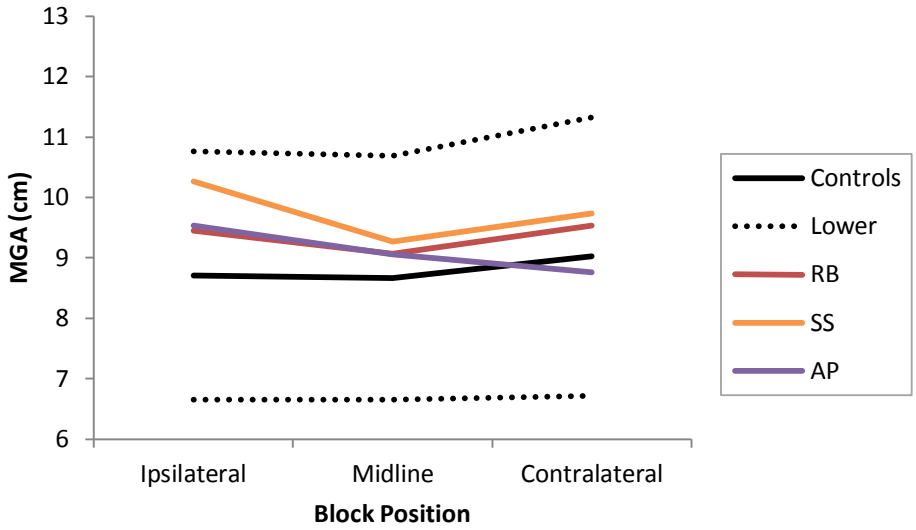


Figure 12.b. *Time to MGA for reaches in Study III: non-dominant hand*

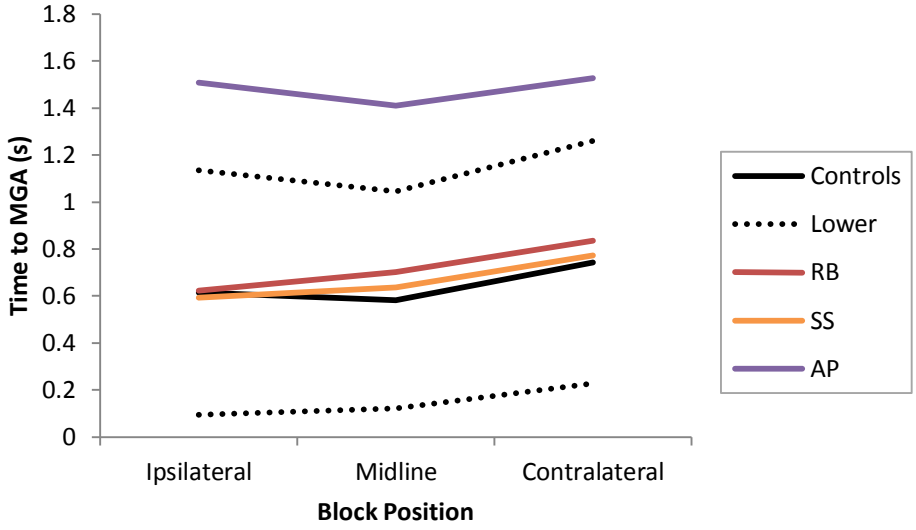


Figure 12.c. *Peak Velocity for reaches Study III: non-dominant hand*

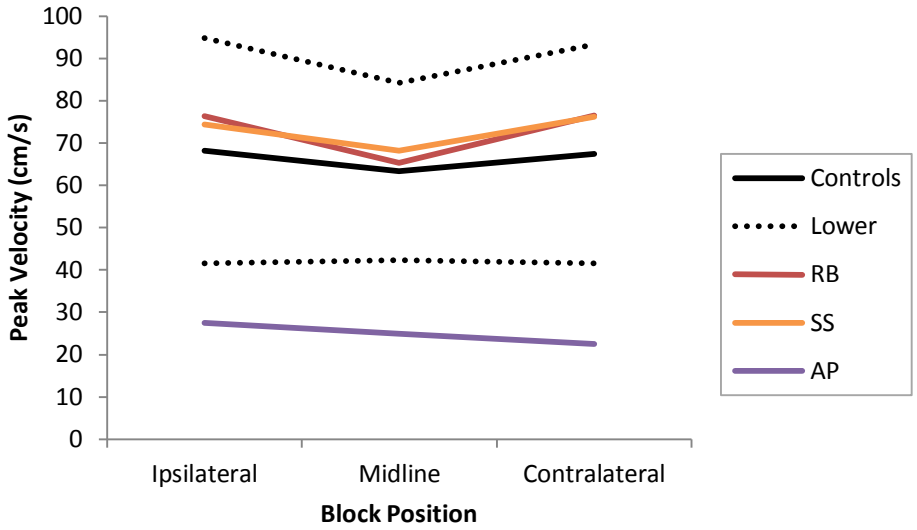


Figure 12.d. *Time to Peak Velocity for reaches in Study III: non-dominant hand*

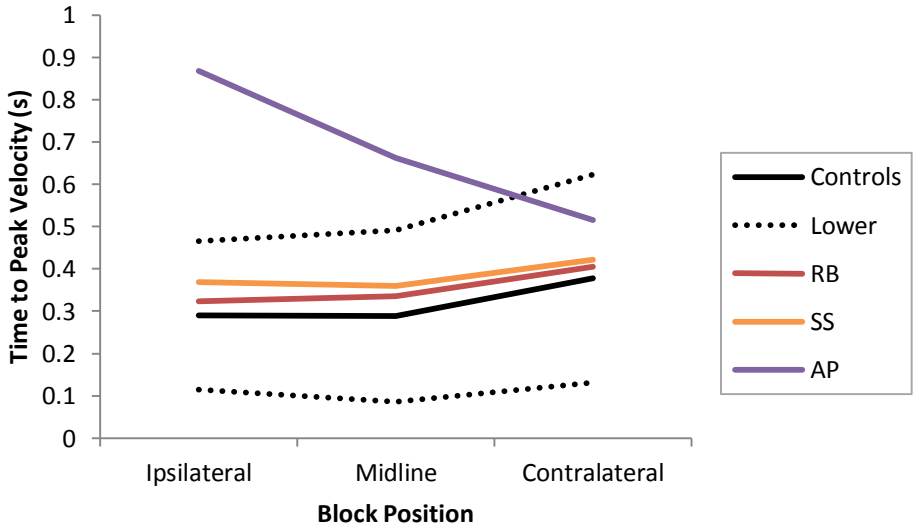


Figure 12.e. *Movement Duration for reaches in Study III: non-dominant hand*

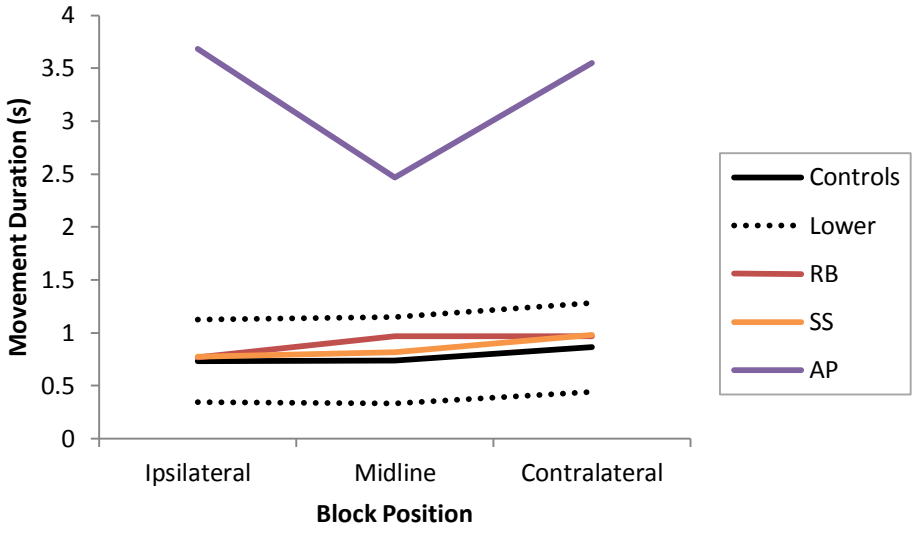


Figure 13.a. *Correlation coefficients for grip scaling in Study III: dominant hand*

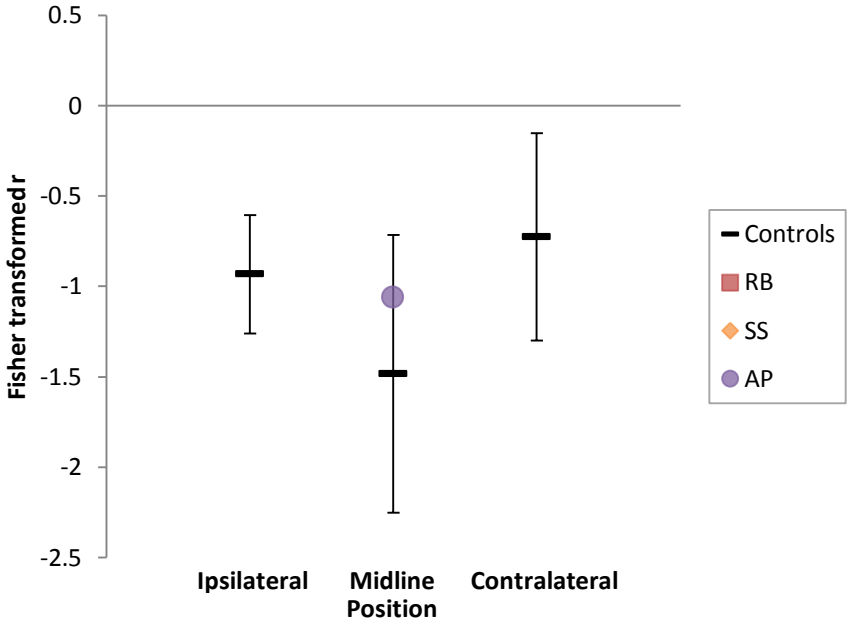
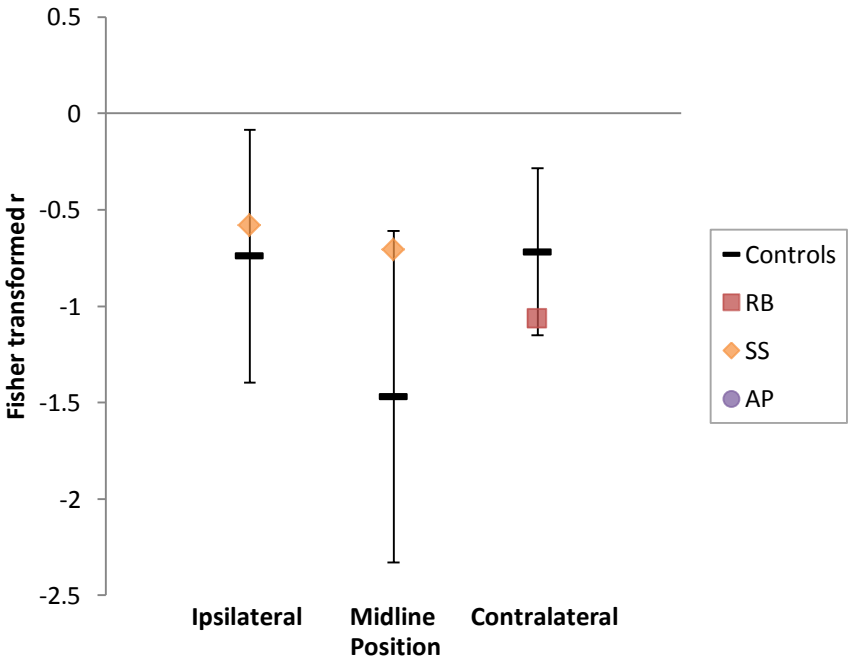


Figure 13.b. *Correlation coefficients for grip scaling in Study III: non-dominant hand*



Note. Data points represent Fisher transformed r values. Coefficients are only included for participants who demonstrated scaling behaviour that was significantly different from zero for that condition. The error bars for the control data represent a 95% confidence interval.

to reaches to the other two locations. Overall MGAs also showed a trend towards being larger for objects on the right, but this difference was not significant at the α=0.05 level ($F(268)=2.833$, $p>0.05$). Finally, post hoc analysis revealed that the difference in peak velocity between locations was driven by slightly higher peak velocities for objects located on the left compared to those at midline.

When reaching for objects at midline, controls seemed to show slightly curved trajectories in the direction of the hand being used (see Figure 14.a). However, these trajectories did not deviate significantly from the idealised straight-line path between initial and final wrist position ($p>0.05$; see Figures 15 and 16). During ipsilateral reaching, in which peripherally-presented objects were positioned on the same side of the body to that of the hand being used, controls exhibited a very similar pattern of behaviour to that seen at midline. Reach paths showed a tendency to curve away from an idealised straight-line path in the direction of the hand being used (see Figure 14.b). This bias was significant for the left hand ($p<0.05$), but not for the right ($p>0.05$). During contralateral reaching, in which peripherally-presented objects were positioned on the opposite side of the body to that of the hand being used, controls once again showed trajectories that did not deviate significantly from an idealised straight-line path to the target ($p>0.05$; see Figure 14.c). To check for magnetic misreaching, the number of reaches that fell close to the fixation point – within a 3cm-radius ROI – was counted. Of the 360 reaches made by controls, only three (<1%) passed through the ROI. Closer inspection of these three reaches revealed that wrist height was maintained high above the surface of the table and there was no decrease in wrist velocity as the hand passed through the ROI. In other words, these rare deviations towards the fixation point simply represented a highly-curved trajectory to the peripheral target, rather than a reach directed specifically towards the fixation point.

Figure 14.a. *Reach paths for objects at midline in Study III*

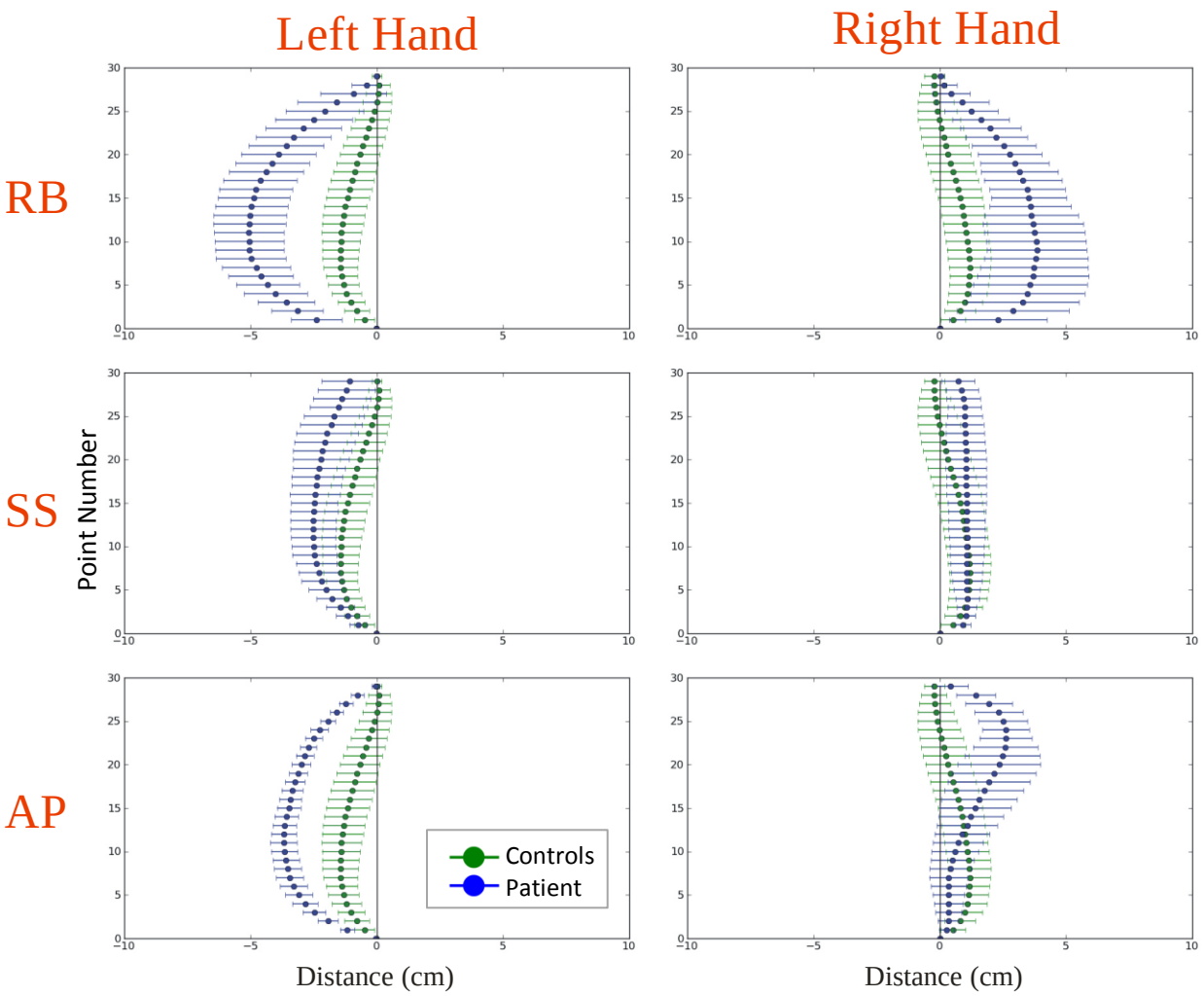


Figure 14.b. *Reach paths for ipsilateral objects in Study III*

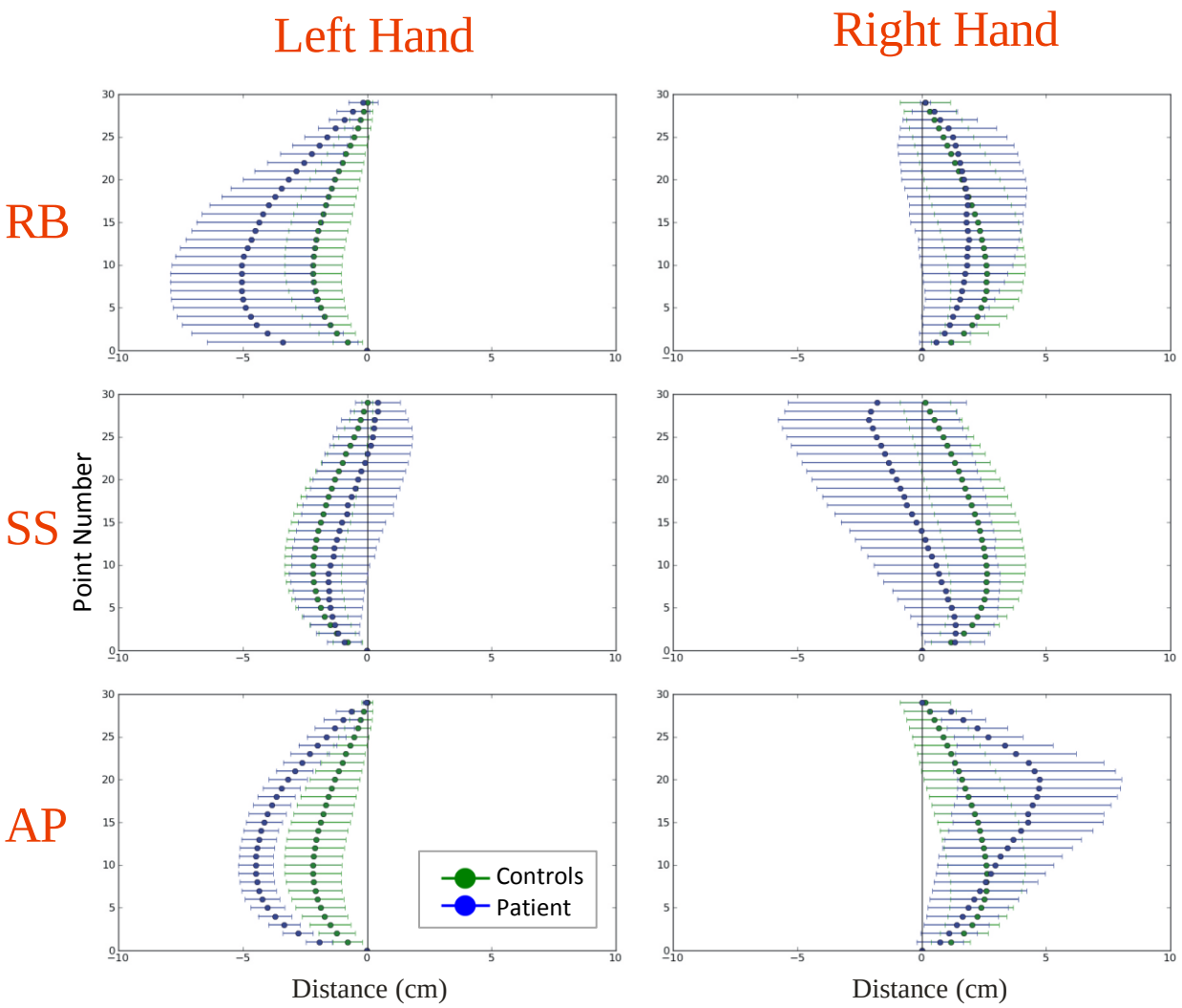


Figure 14.c. *Reach paths for contralateral objects in Study III*

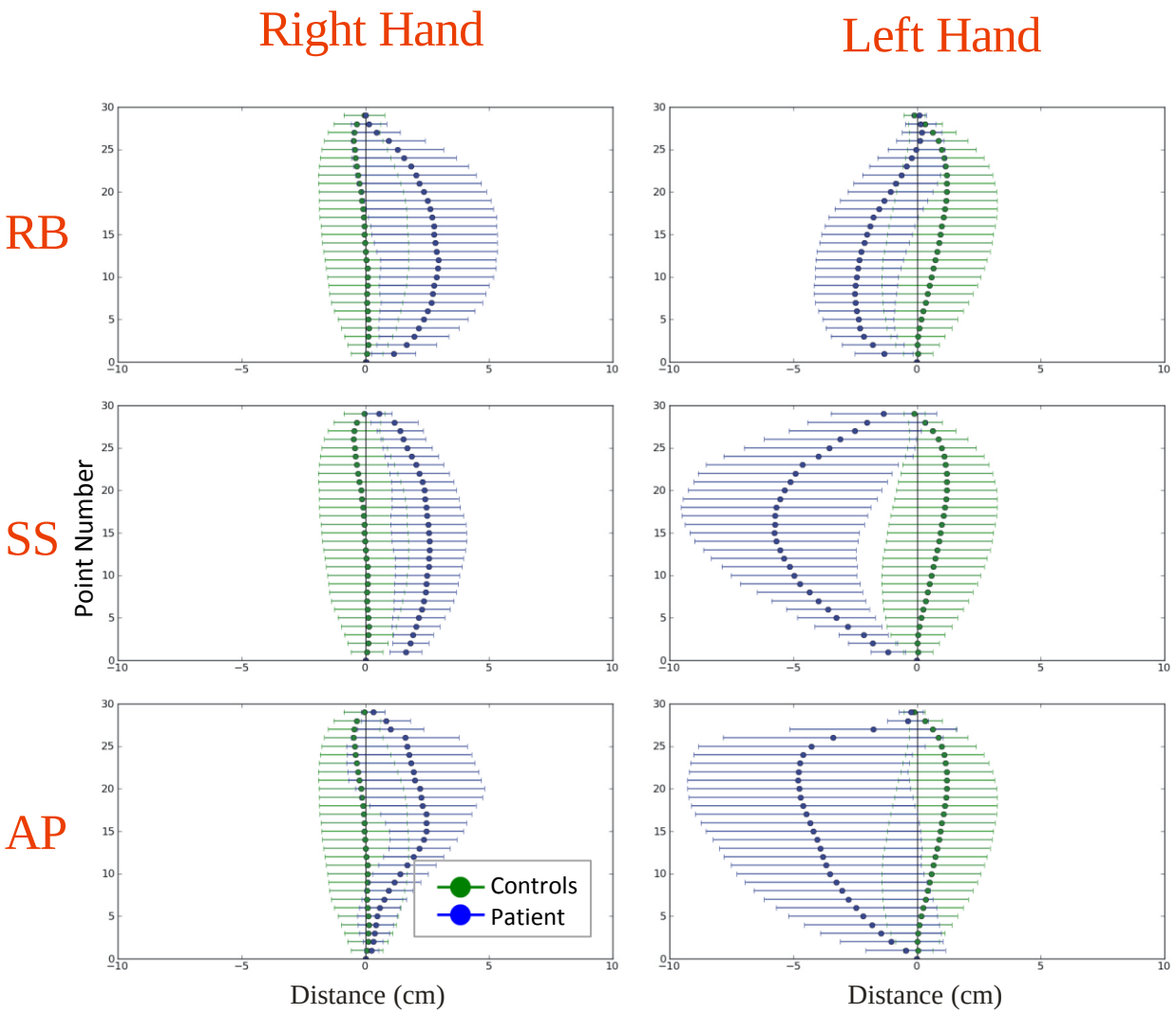


Figure 15.a. *Leftward reach path deviation in Study III: right hand*

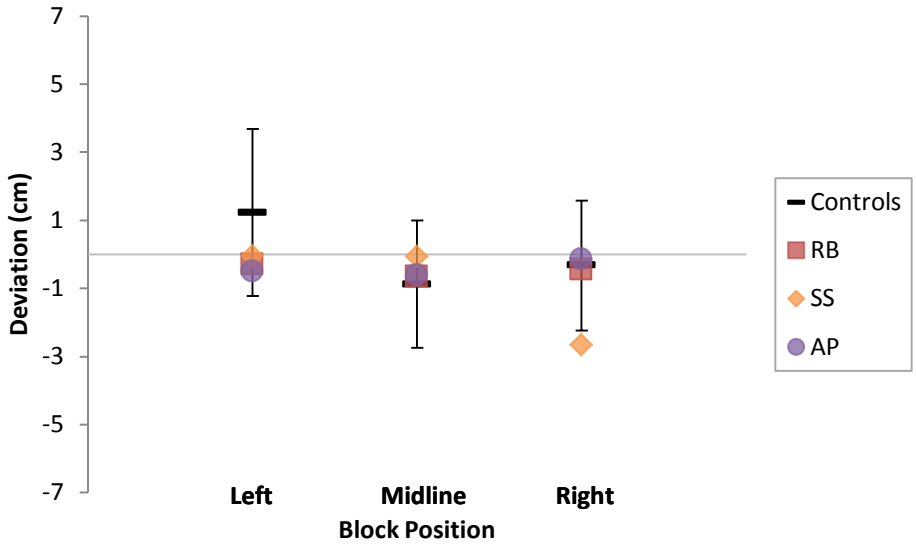


Figure 15.b. *Rightward reach path deviation in Study III: right hand*

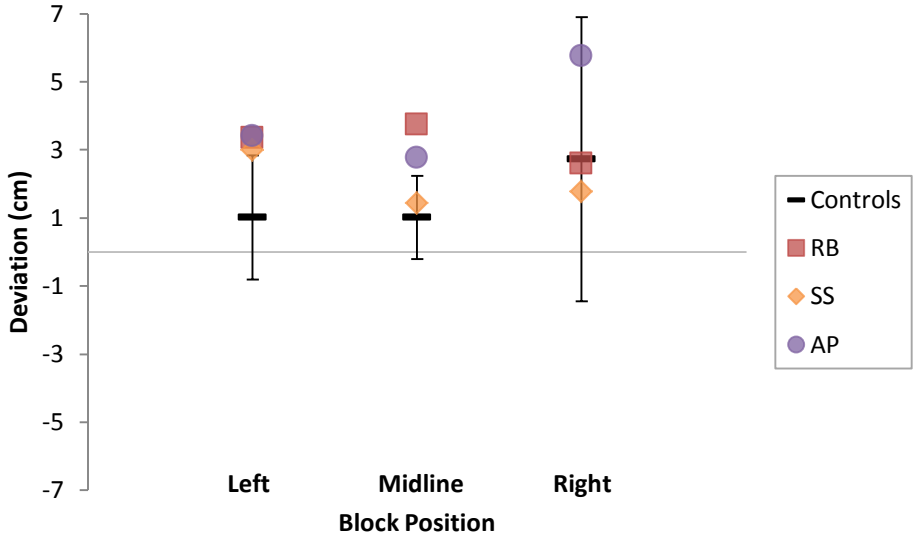


Figure 16.a. *Leftward reach path deviation in Study III: left hand*

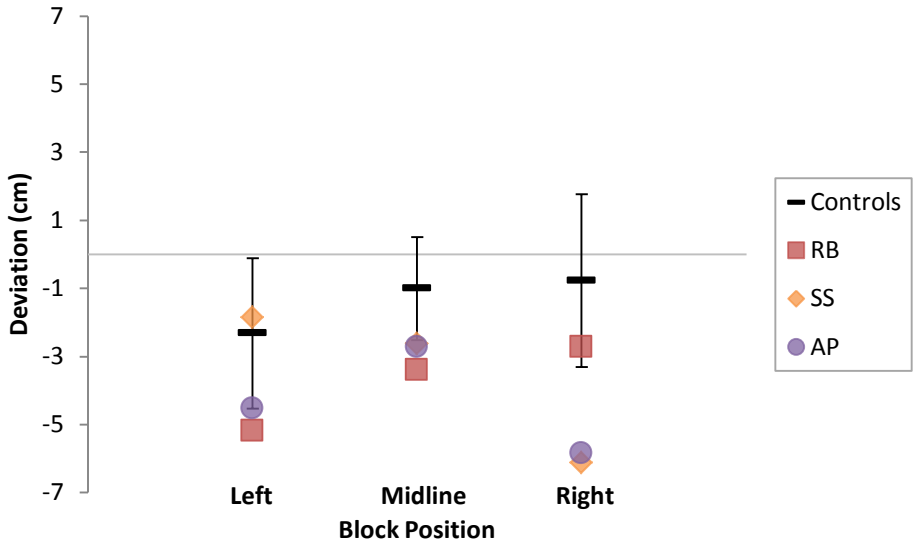
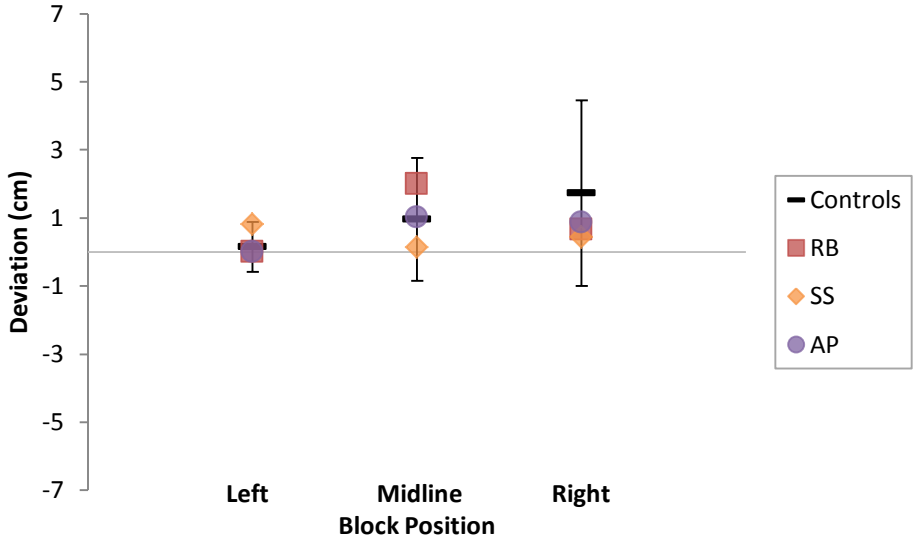


Figure 16.b. *Rightward reach path deviation in Study III: left hand*



Not surprisingly, controls were very precise with their grasps regardless of object location. Compared to other conditions, healthy individuals showed a slight reduction in accuracy when reaching to contralateral targets with their non-dominant, left hands. In this condition, controls had to make small adjustments to their grasps on roughly 12% of trials. For all other hand/location combinations, minor grasp corrections following object contact were observed on less than 5% of trials (see Figures 17.a and 18.a).

RB. RB showed no evidence of scaling behaviour when using either her right ($p>0.05$) or left hand ($p>0.05$) to grasp objects at midline (see Tables 3 and 4 for regression results). She also failed to scale her grip to the size of the object with either hand to objects located in her left visual hemifield ($p>0.05$), and with her right hand to objects presented in her right visual hemifield ($p>0.05$). She did however show significant scaling with her left hand to objects in her right visual hemifield ($p<0.05$). This scaling was no different from that of controls for the same condition ($p>0.05$; see Figure 13.b).

Like controls, RB showed no difference in the kinematics of her reaches between her right and left hands ($p>0.05$). When using her right hand, RB's overall MGAs were larger for objects located at her midline than those located in her visual periphery ($F(42)=5.135$, $p<0.05$; see Figure 11 for dominant hand kinematic comparisons), though this difference was only significant between objects at midline and objects on the right. She also showed longer reaches for objects at midline versus the periphery ($F(43)=3.655$, $p<0.05$), and a lower peak velocity for objects at midline compared to those on the right ($F(43)=6.881$, $p<0.05$). Comparing these results to controls, we see that RB's time to MGA, time to peak velocity, and movement time were all longer than controls for objects at midline ($p<0.05$). RB's time to peak velocity was also

Figure 17.a. *Grasping precision in Study III: Controls right hand*

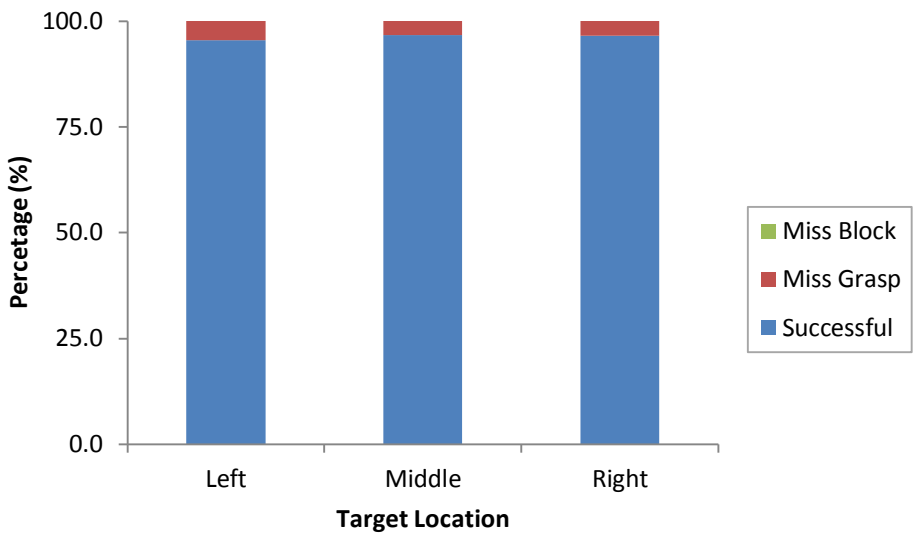


Figure 17.b. *Grasping precision in Study III: RB right hand*

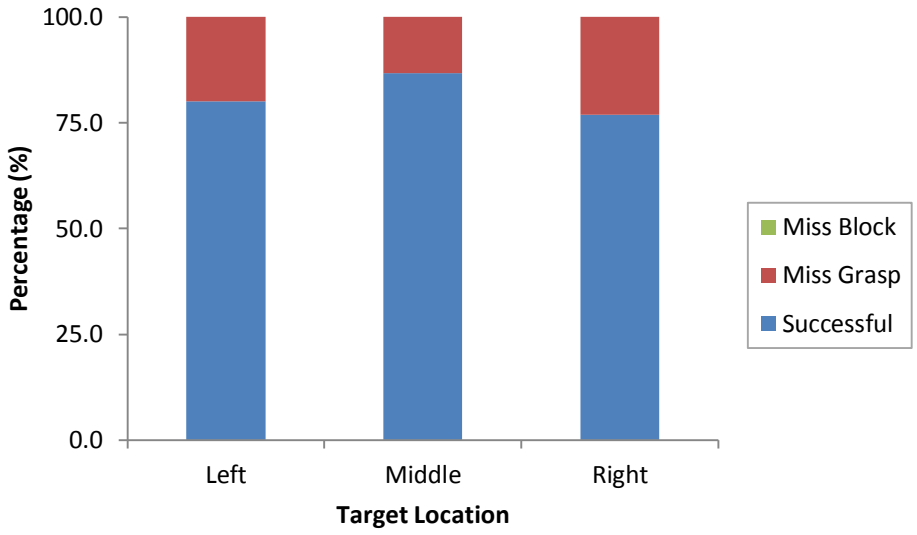


Figure 17.c. *Grasping precision in Study III: SS right hand*

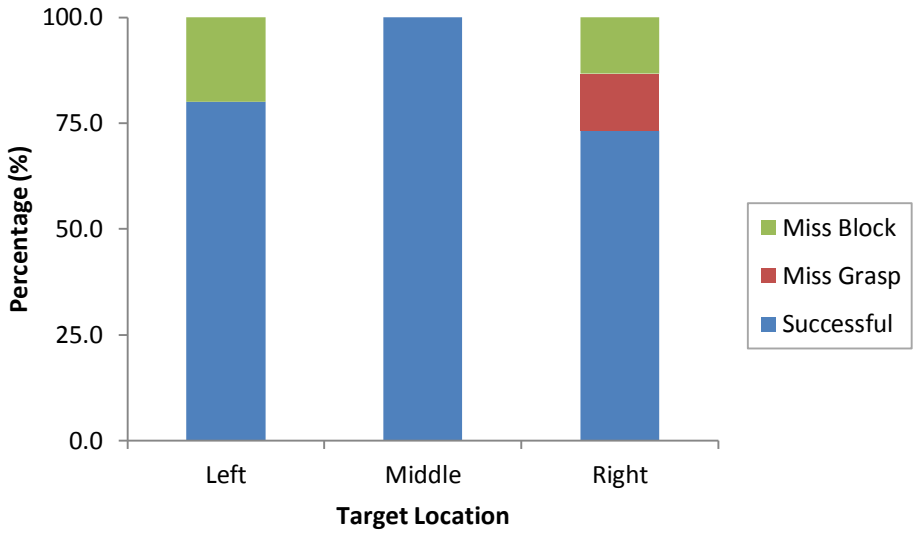


Figure 17.d. *Grasping precision in Study III: AP right hand*

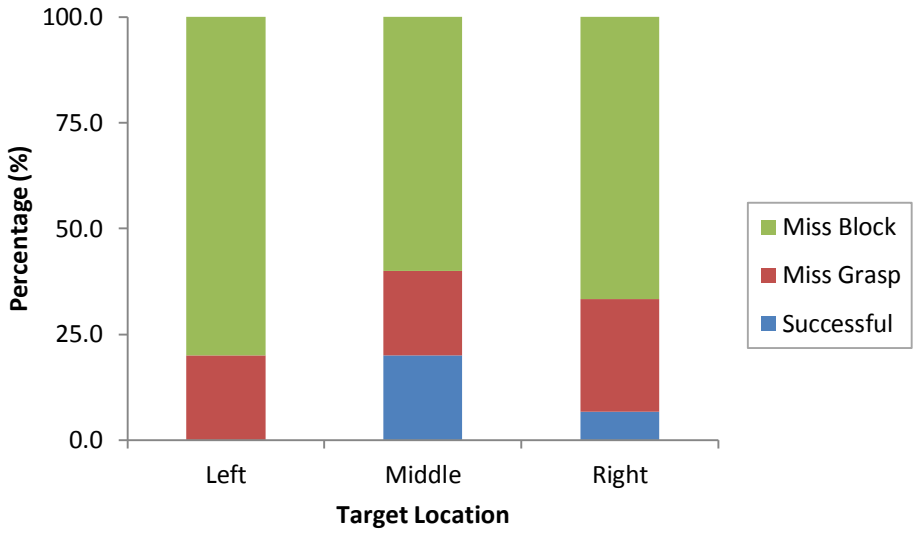


Figure 18.a. *Grasping precision in Study III: Controls left hand*

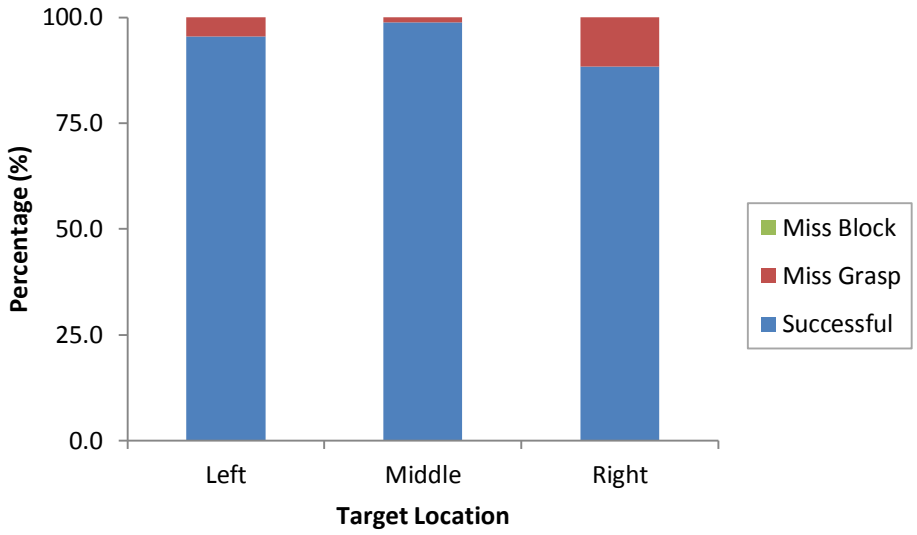


Figure 18.b. *Grasping precision in Study III: RB left hand*

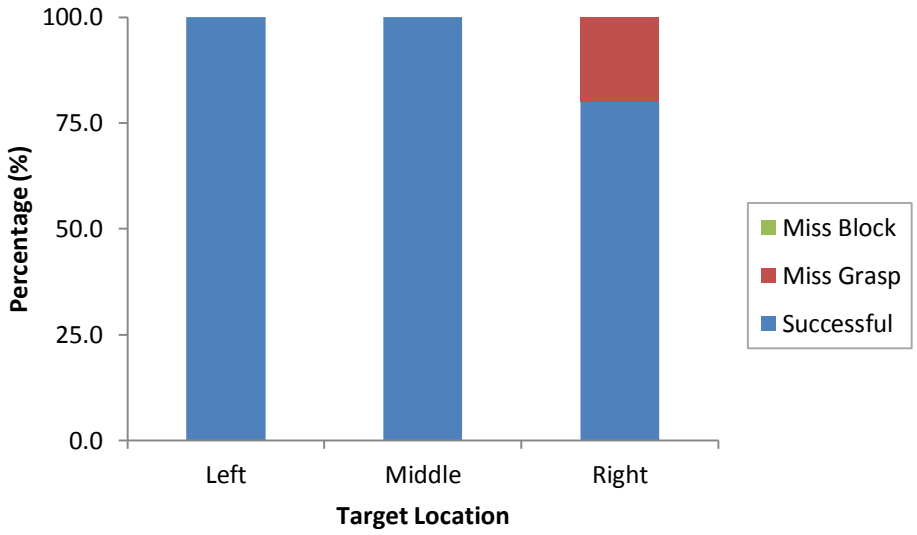


Figure 18.c. *Grasping precision in Study III: SS left hand*

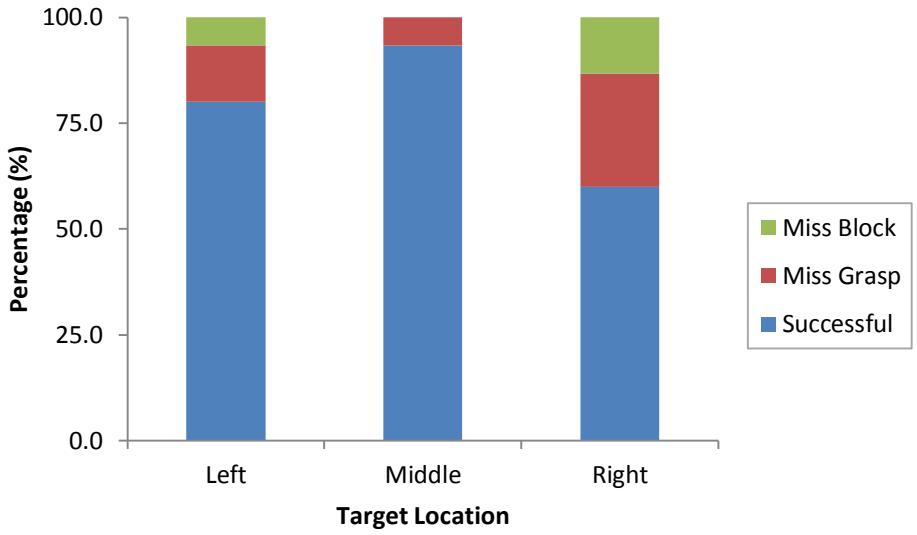
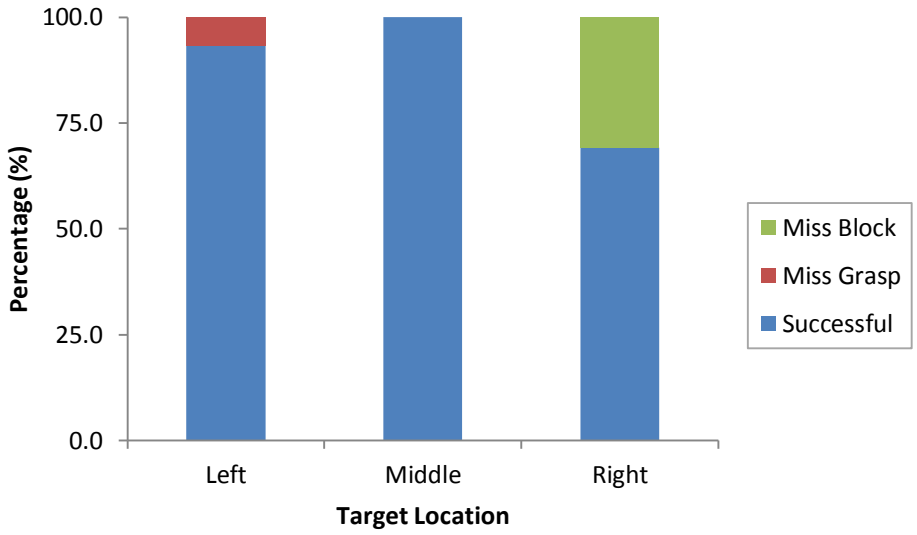


Figure 18.d. *Grasping precision in Study III: AP left hand*



longer than controls for objects on the right ($p<0.05$). With her left hand, RB showed no significant difference in overall MGA, time to MGA, or time to peak velocity across positions ($p>0.05$; see Figure 12 for non-dominant hand kinematic comparisons), but did show a lower peak velocity ($F(44)=4.463$, $p<0.05$) and longer movement time ($F(44)=3.545$, $p<0.05$) for objects at midline compared to those in her visual periphery. None of RB's kinematic measures for left-handed reaches were different from controls for objects at any of the three locations ($p>0.05$).

Looking at the reach trajectories for these same grasps (see Figure 14 for averaged reach paths), RB showed reach paths for objects at midline that deviated significantly more from the idealised straight-line path than those of controls with both hands ($p<0.05$; see Figures 15 and 16 for deviation comparisons). Specifically, her trajectories were biased toward the side of the hand being used. For ipsilateral reaches, RB's right-hand paths were very similar to controls ($p>0.05$), but she showed a significant deviation from the reach-path made by controls with her left hand ($p<0.05$) in the direction of the hand being used. For contralateral reaches, RB showed a tendency to reach towards the point of fixation with both hands, though this deviation was only significantly different from controls with her right hand ($p<0.05$). Considering only grasps to peripheral targets, three (5%) of RB's reach-paths passed through the fixation point ROI. A kinematic analysis of these three reaches revealed that as her hand passed through the ROI, her wrist was held high above the surface of the table and there was no decrease in wrist velocity. Therefore, like controls, the deviation towards the fixation point simply represented a highly-curved trajectory to the peripheral target, rather than a reach directed specifically at the fixation point.

In general, RB's grasps were fairly precise (see Figures 17.b and 18.b). At midline, RB's grasps required minor grip corrections on two of the 15 grasps made with her right hand, and

none of the grasps with her left hand. She made slightly more errors when reaching for peripheral targets, requiring minor grip corrections on three grasps each to objects on the right and left when using her right hand, as well as three grasps to objects on the right with her left hand.

MTB. MTB was unable to complete this task. While she had no trouble grasping objects placed at her midline, she found it impossible to execute grasps to objects in her periphery. When prompted to reach to peripheral targets, she would sit for a long time without moving, staring intently at the fixation point. When again prompted to reach to the target, she would sometimes reply that it was "too difficult". Often she would move her hand two or three centimeters from the start button, keeping her fingers together, and place it back down on the table. During these trials, I would often ask if she could in fact see the target object. She would always respond that she could, or at least that she thought she could. After attempting a number of trials, I determined that MTB was not going to be able to finish. I decided to start the experiment again, this time placing the peripheral objects 6cm from the fixation point rather than 12cm. This change made no difference to MTB's behaviour. She reported that it was now easier to see the objects, but she could still not even attempt to grasp them. At this point, she was evidently very frustrated and becoming upset with her inability to perform the task. To avoid any unnecessary stress, I ended the experiment prematurely. For this reason, no data can be presented for MTB with respect to peripheral targets.

SS. SS failed to show appropriate grip scaling to objects located at his midline with his right hand during the peripheral task ($p>0.05$; see Tables 3 and 4 for regression results). This contrasts with his behaviour in Study I, in which SS showed evidence of grip scaling at midline under normal viewing conditions. However, despite showing significant scaling in Study I, his

scaling was weaker than controls, so it is not a complete surprise that he also showed visuomotor deficits at midline in Study III. These visuomotor deficits were also apparent for objects located in the periphery, as SS failed to show grip scaling with either hand to objects located in his right visual hemifield ($p>0.05$), or with his right hand to objects located in his left visual hemifield ($p>0.05$). He did, however, show significant scaling with his left hand for objects located at his midline ($p<0.05$), which was no different from controls ($p>0.05$; see Figure 13.b), and in his left visual hemifield ($p<0.05$), which was also no difference from controls ($p>0.05$).

SS produced much larger grip apertures with his right hand (11.57cm) compared to his left (9.76cm; $t(88)=8.206$, $p<0.05$), but it took him significantly longer to reach MGA with his left hand (0.67s) compared to his right (0.59s; $t(88)=2.682$, $p<0.05$). However, his peak velocity, time to peak velocity, and movement duration were no different between his hands ($p>0.05$). When using his dominant, right hand, SS produced larger overall MGAs for reaches made to objects located in his periphery compared to those at midline ($F(44)=8.116$, $p<0.05$; see Figure 11 for dominant hand kinematic comparisons). It also took him longer to reach MGA ($F(44)=3.655$, $p<0.05$), longer to reach peak velocity ($F(44)=4.273$, $p<0.05$), and longer to complete his movement ($F(44)=4.613$, $p<0.05$) when reaching to objects on the left compared to the middle. Other than MGA, none of SS's right-hand kinematic values were significantly different from controls ($p>0.05$). When using his left hand, SS showed a larger overall MGA for objects on the left compared to those at midline ($F(44)=3.397$, $p<0.05$; see Figure 12 for non-dominant hand kinematic comparisons), longer time to MGA for objects on the right compared to the other two locations ($F(44)=7.198$, $p<0.05$), higher peak velocities for objects in the periphery compared to midline ($F(44)=6.372$, $p<0.05$), and longer movement times for objects on the right ($F(44)=7.927$, $p<0.05$). As with RB, none of SS's left-hand kinematic values were significantly different from controls ($p>0.05$).

At midline, SS showed reach trajectories that were much more comparable to controls than either RB or AP (see Figure 14 for averaged reach paths). However, the reach-path for his left hand did deviate significantly from that of controls towards the hand being used ($p<0.05$; see Figures 15 and 16 for deviation comparisons). For ipsilateral reaches, SS showed a significant departure from controls with his right hand, reaching closer to the point of fixation ($p<0.05$). He showed a similar trend towards the fixation point with his left hand, but the effect did not reach significance ($p>0.05$). This fixation point bias was even more apparent for contralateral reaches, where SS's reach paths showed a significant departure from controls towards the fixation point with both his right and left hands ($p<0.05$). Considering only grasps to peripheral targets, nine (15%) of SS's reach-paths passed through the fixation point ROI. Looking at the kinematics of these atypical trajectories, we see that in five of SS's aberrant reaches, wrist height and velocity decreased as the hand entered the ROI, indicating a significant deviation from a normal peripheral grasp trajectory. In other words, SS demonstrated reaches that were drawn towards the fixation point to such an extent that the kinematics of his trajectory resembled those of a reach made to a central target. In fact, in the majority of these reaches, SS actually touched his fingers to the surface of the table at the fixation point, before 'correcting' his movement and accelerating towards the peripheral target.

SS was highly accurate when grasping objects at midline (see Figures 17.c and 18.c), requiring adjustments to his grip for none of the 15 grasps made with his right hand (see Figure 16.c), and only one of the 15 grasps made with his left hand (see Figure 18.c). SS's accuracy dropped for objects located in his visual periphery, and this drop was more distinct than that seen for RB. When using his dominant, right hand, SS missed the block completely on three of the 15 reaches made to objects on his left, and two of the 15 reaches to objects on his right. He also made minor grip corrections on an additional two reaches to objects on the right. With his

left hand, SS required minor grip corrections during two of his 15 grasps to objects on his left, and four of his 15 grasps to objects on his right. Additionally, he missed the block completely on one trial to the left and two trials to the right.

AP. AP demonstrated similar grasping behaviour to that seen in the delayed open-loop condition in Study I, showing accurate grip scaling for objects located at her midline with her dominant, left hand ($p<0.05$; see Tables 3 and 4 for regression results), which was no different to the scaling of controls with their dominant hands ($p>0.05$; see Figure 13.a). In contrast, she failed to show scaling when reaching for objects located in either peripheral hemifield with her left hand ($p>0.05$), and in any location with her right hand ($p>0.05$). In other words, AP's ability to scale her grasps was limited to actions performed with her left hand to objects she was allowed to foveate.

AP had a great deal of difficulty performing precise movements with her right hand. This can be seen by looking at her reach kinematics, where there were large differences between her two hands; she had smaller grip apertures ($t(86)=7.467$, $p<0.05$), longer times to MGA ($t(86)=4.037$, $p<0.05$), slower peak velocities ($t(66)=10.614$, $p<0.05$), longer times to peak velocity ($t(68)=6.305$, $p<0.05$), and longer overall movements times ($t(86)=6.061$, $p<0.05$) with her right hand compared to her left. When using her dominant hand, AP showed greater difficulty reaching to objects located in her right visual periphery than the other two locations (see Figure 11 for dominant hand kinematic comparisons). For objects on the right, she showed longer times to MGA ($F(42)=16.634$, $p<0.05$), lower peak velocities ($F(42)=27.146$, $p<0.05$), longer times to peak velocity ($F(42)=17.239$, $p<0.05$), and longer movement durations ($F(42)=57.465$, $p<0.05$) compared to the other two locations. Conversely, her MGAs were no different between midline and the right periphery ($p>0.05$), but were larger for objects in the

left periphery compared to midline ($F(42)=10.982$, $p<0.05$). Comparing these data to controls, we see that AP seemed to struggle when reaching for contralateral objects with her dominant hand, having a longer time to MGA, lower peak velocity, and much longer movement durations than controls ($p<0.05$). Additionally, for ipsilateral and centrally-placed objects, AP's peak velocity was noticeably slower and movement durations much longer than controls. However, this effect was only significant for movement duration for objects at midline ($p<0.05$). When using her right hand, AP showed no difference in MGA or time to MGA across positions, but showed a lower peak velocity ($F(44)=4.364$, $p<0.05$; see Figure 12 for non-dominant hand kinematic comparisons) and shorter time to reach peak velocity ($F(44)=9.851$, $p<0.05$) for objects on the left compared to those on the right. Additionally, her movement times were longer for objects in the periphery compared to those at midline ($F(4s)=6.959$, $p<0.05$). As might be expected from the extreme differences in reach kinematics between her right and left hands, AP showed drastic differences for reaches with her non-dominant hand compared to controls. She exhibited longer movement durations, lower peak velocities, and longer times to MGA than controls for objects at all locations ($p<0.05$). Additionally, she showed longer times to reach peak velocity for ipsilateral and centrally-located objects ($p<0.05$).

AP's reach paths deviated from controls with both hands for objects located at her midline ($p<0.05$; see Figure 14 for averaged reach paths). As with the other patients, her reaching bias was in the direction of the hand being used (see Figures 15 and 16 for deviation comparisons). For ipsilateral reaches, AP showed a trend towards reaching away from the point of fixation compared to controls. However, this effect was only significant for reaches made with her left hand ($p<0.05$). For contralateral reaches, AP showed the same pattern as SS, reaching closer to the point of fixation than controls with both hands ($p<0.05$). In order to determine whether these results were purely a consequence of AP's handedness, the path

comparisons were repeated, comparing AP's path deviations for her left hand to controls' right hands, and vice versa. Instead of left and right hands reaching to left, midline, or right targets; conditions were now dominant and non-dominant hands reaching to ipsilateral, midline, or contralateral targets. Following this analysis, the results for AP's reaches to midline and contralateral targets did not change; her reaches at midline were biased towards the effector hand, and her contralateral reaches were biased towards the fixation point. However, she no longer showed a path bias with her left hand for ipsilateral targets, but instead showed a bias with her right hand for ipsilateral targets. As before, this reach bias was away from the point of fixation. This change in result was driven by the much higher variation in reach paths made by controls for the ipsilateral condition with their dominant, right hands compared to their non-dominant, left hands. Considering only grasps to peripheral targets, eight (13%) of AP's reach-paths passed through the fixation point ROI. In a similar manner to SS, the kinematics of AP's reaches through the ROI showed that in four of these eight reaches, AP's wrist height and velocity decreased as her hand entered the ROI. Additionally, her fingers occasionally touched the table during these reaches, as if she were executing a grasp to the fixation point itself rather than the peripheral target.

As might be expected from her kinematic data, AP's ability to accurately grasp objects without the need for grip or reach corrections was relatively intact when using her left hand (see Figure 18.d), but severely impaired with her right hand (see Figure 17.d). Specifically, AP was highly successful at executing accurate grasps with her left hand to objects at midline and in her left visual field. It is perhaps not surprising that she was accurate with her dominant hand at midline, since her kinematics and grip scaling remained relatively intact for this condition. A similar case may be made for her left-handed grasps to ipsilateral targets, though she did not show appropriate scaling in this condition. Interestingly, however, she did show larger overall

MGAs than controls for ipsilateral grasps with her left hand, so she may well have used a similar strategy to SS – exaggerating her grip aperture to ensure appropriate object contact while dealing with impaired visuomotor control. AP's grasps with her left hand to contralateral targets were not as successful, given that she missed the block completely on over 30% of reaches. Having already established from her kinematic data that AP struggled with this condition, this result is perhaps not surprising. AP's ability to accurately guide her right hand to target objects in any location was remarkably poor. In fact, only four of her 45 right-handed grasps did not require correction, and she missed the block completely in 31 of the remaining 41 trials.

Discussion.

Controls. Controls showed accurate grip scaling behaviour with both their dominant and non-dominant hands to objects located at their midline and in their visual peripheries. Additionally, reaches made to peripheral targets were generally very precise, as grasps rarely required corrections to hand or finger positions during the trail. These data demonstrate controls' ability to obtain precise information regarding target properties, such as size and location, from objects located in peripheral vision. Although controls' non-dominant hands achieved a slightly lower peak velocity than their dominant hands, all other kinematic variables were no different between the two. Furthermore, controls proved to be highly adept at performing accurate reaches with their non-dominant hands. Object location did have an effect on visuomotor performance, as contralateral reaches with both hands tended to take longer and have larger grip apertures.

It has previously been documented during visuomotor tasks to peripheral targets that healthy participants produce movements that are biased away from the point of fixation (Henriques et al., 1998; Henriques & Crawford, 2000; Khan et al., 2004). The control group in

this experiment did show a trend towards this behaviour, but this bias was only significant for left handed reaches to ipsilateral stimuli. For the most part, controls' reach paths were not significantly different from an idealised straight-line path to the objects. For midline targets in particular, this behaviour is typical, as humans have been shown to naturally generate straight reach paths when directed to move their hands deliberately to a target (Abend, Bizzi, & Morasso, 1982). Furthermore, it is difficult to conclude that the path curvature seen in the left hand ipsilateral condition is actually an anti-fixation bias rather than a bias towards the side of hand being used. This 'effector-hand bias' explanation actually seems more likely given the trend towards such behaviour even for reaches to centrally located targets. The absence of an anti-fixation point bias in the current study compared to previous studies may be due to differences in task demands between experiments. For example, many of the studies that have documented a bias away from the point of fixation required participants to point to peripheral targets rather than grasp objects in peripheral vision. Additionally, the movements made by participants in these studies were often rapid, time-sensitive movements, as opposed to the slower, reach-to-grasp movements made in the current study. As a result, the anti-fixation point bias reported in previous studies was often recorded as a 'horizontal overshoot' of the target location rather than a trajectory path that curves away from the point of fixation.

RB. RB once again showed an inability to scale her grip to the size of the block under visual guidance. This deficit is present when using both her left and right hands, for objects located at her midline as well as in her visual periphery. The presence of normal scaling behaviour with her left hand to objects in her right visual field suggests that some weak remnant of her scaling ability remains. In Study I, we saw that RB showed counterintuitive behaviour when reaching for objects she couldn't see: her overall MGA was smaller during open-loop grasping compared to the visually-guided condition. This is strange because one

would expect MGA to increase when uncertainty regarding the target increases, as is the case when vision is removed. RB showed similarly unexpected behaviour in the current study. When using her right hand, RB's overall MGA was smaller when reaching for peripheral targets compared to those at midline. Since peripheral targets were not foveated, information regarding object properties would be less detailed than for objects at midline. Indeed, healthy participants are generally less precise when reaching to peripheral targets than foveated targets (Himmelbach et al., 2006). This increased uncertainty regarding target information should result in a compensatory increase in MGA. RB, however, does the opposite. She also exhibits a higher peak wrist velocity and shorter movement time for peripheral targets compared to those at midline with both her right and left hands. A higher peak velocity is not particularly unusual, since the peripheral targets are farther away from the start button than the objects at midline, and previous research has shown that maximum velocity increases with target distance (Jeannerod, 1984; Gentilucci, Chieffi, Scarpa, & Castiello, 1992). Indeed, similar behaviour was seen in our control group. However, the same cannot be said for shorter movement times to peripheral targets. As with MGA, we would expect a more conservative approach to be taken when target uncertainty is increased, which in this case would manifest itself as an increased movement time. Indeed, this is the behaviour exhibited by controls to peripheral targets. Once again, however, RB shows the opposite pattern of behaviour to what is expected. Furthermore, RB's time to MGA, time to peak velocity, and movement time were all longer than controls for objects at midline, but generally similar to controls for objects in the periphery. Why would RB's kinematics fall outside the normal range for objects she was allowed to foveate, but improve for reaches to peripheral targets? Perhaps, for objects at midline, RB was making an extra effort to use incoming visual information to guide and correct her grasps, resulting in slower, more careful reaches. Meanwhile, for objects in her periphery, this strategy may have been either too

effortful or simply too difficult to employ due to imprecise visual feedback being provided to her as a result of damage to parietal areas. If this were the case, RB may well have abandoned any attempts to compensate for her failing visuomotor system by using additional visual guidance, and simply reached out 'naturally', hoping for the best.

For objects at midline, RB's reach-paths were curved compared to controls with both her right and left hands. Path curvatures were in the direction of the hand being used, i.e. her wrist curved to the right of midline when using her right hand and vice versa. This behaviour represents an inefficient reach strategy, and suggests that her visuomotor system is not programming reach trajectories in the most effective manner. RB showed similar behaviour when asked to reach to peripheral targets: her path was excessively curved compared to controls with her right and left hands to objects on the left. Once again, both curvatures were in the direction of the hand being used. As such, RB did not demonstrate a reaching bias towards the point of fixation. This conclusion is reinforced by the fact that only three of her 60 peripheral reaches passed through the 3cm-radius ROI around the fixation point, and the fact that these reaches showed no obviously abnormal reach kinematics.

MTB. MTB's inability to reach out and pick up objects in her periphery is intriguing. Based on her performance in Studies I and II, she clearly has the motor skills available to perform such an action, suggesting that her inability is not the result of a physical limitation. The possibility that it's a visual problem is much greater, given MTB's poor peripheral vision; visual field tests revealed that MTB has almost no vision in her left visual field, while her right visual field is more intact. These results seem to match MTB's behaviour, as she had more difficulty initiating grasps to objects on the left than she did for objects on the right. However, visual dysfunction doesn't seem to be the whole story. Firstly, MTB still claimed to be able to see the

objects presented in her left visual field. Even though this claim cannot be substantiated, the question remains: If she thought she could see an object, why could she not initiate a reach towards it? Secondly, given that vision in her right visual field is relatively intact, why did she have so much difficulty initiating reaches to objects presented in that location?

An inability to initiate motor actions can be indicative of the presence of various neurological disorders, such as ideomotor apraxia, ideational apraxia, or akinesia. However, these explanations for MTB's behaviour can effectively be ruled out thanks to her intact ability to execute accurate grasps to objects at midline – seen in Studies I and II, as well as her ability to pantomime object use – observed during administration of the Edinburgh Handedness Inventory. The most reasonable explanation, therefore, is a combination of visual field defects and the presence of optic ataxia. It seems likely that MTB could not see the target objects very well, if at all, when they were presented in her left visual periphery, despite her claims to the contrary. This fact, combined with MTB's obvious desire to perform well on the task, made her extremely hesitant to attempt grasps to objects whose size and location was unclear. Based on the visual field tests performed by her ophthalmologist, it seems that MTB's vision for objects located in her right visual periphery should be relatively intact. This suggests that MTB's inability to initiate reaches to objects in that location is a result of severe optic ataxia rather than basic visual or motor deficits.

SS. SS demonstrated evidence of more extensive visuomotor deficits in this Study than he did in Study I, despite both tests being administered within a one-week period. Most dramatically, in Study III, he failed to scale his grasps to the size of objects with his dominant, right hand when targets were placed at his midline. These results are not completely inconsistent, however, given that SS's scaling ability, though present in Study I, was less robust

than that of controls. SS's inability to accurately scale grasps with his right hand was not limited to objects at midline, as he showed no evidence of scaling behaviour with his dominant hand to objects in his visual periphery either. SS's visuomotor control for actions with his left hand actually seemed much better than for his right. He showed accurate scaling behaviour with his non-dominant hand for objects at midline and in his left visual field, though this ability was not present for objects on the right.

SS's kinematic measures did not reveal anything too unusual. In three out of four conditions, his MGA was wider for objects in the periphery compared to those at midline, which is what would be expected when target uncertainty is increased. One intriguing result is that overall MGAs with his right hand were much larger than that of controls, whereas those with his left hand were no different. This much larger MGA was also seen with his right hand in Study I. While it still holds that direct comparisons with regards to MGA cannot be made, given the unaccounted for differences between subjects' finger sizes, this difference between SS's hands is curious. Considering the deficits in scaling seen with his right hand, it is possible, though speculative, that the reason for these much larger MGAs is that he is compensating for deficiencies in his visuomotor system by 'overshooting' the required grip size. Meanwhile, the visuomotor control of his left hand seems more intact, so there is no need for exaggerated grip apertures.

Unlike RB, SS showed a definite bias toward the point of fixation during peripheral reaches. This bias was more pronounced for objects in his right visual field, as his reaches with both hands to objects in that location deviated significantly toward the point of fixation compared to controls. In support of the presence of a fixation bias is the observation that nine (15%) of SS's peripheral reaches passed within 3cm of the fixation point. Considering that less

than 1% of controls' grasps passed through the same ROI, this percentage suggests abnormal behaviour. Looking at the kinematics of these atypical trajectories, we see that in five of SS's aberrant reaches, wrist height and velocity decreased as the hand entered the ROI, indicating a significant deviation from a normal peripheral grasp trajectory. In other words, SS demonstrated reaches that were drawn towards the fixation point to such an extent that the kinematics of his trajectory resembled those of a reach made to a central target. In fact, in the majority of these reaches, SS actually touched his fingers to the surface of the table at the fixation point, before 'correcting' his movement and accelerating towards the peripheral target. This behavior closely mirrors the phenomenon of "magnetic misreaching", as reported by Carey and colleagues in a patient with optic ataxia (Carey, Coleman, & Della Sala, 1997).

Despite SS's lack of grip scaling with his right hand at midline, he was highly accurate in his ability to execute a successful grasp without correction. This success may well be due to the much larger grip apertures he employed with his right hand compared to controls. By using a large-grip strategy, SS seemed to be able to mitigate his visuomotor difficulties and execute successful grasps with his preferred hand at the expense of the more efficient grip-scaling behaviour seen in controls. Unfortunately, this strategy did not seem to work as well for SS when he was not permitted to foveate the target object. In each of the four peripheral conditions, SS missed the block completely on at least one reach and required grip corrections on additional trials. This difficulty was particularly apparent for objects in his right visual periphery, where corrections were required in almost 40% of all reaches with both hands.

AP. In Study I we saw that AP was able to accurately scale her grip with her dominant, left hand to objects at midline. Although this same behaviour was observed in Study III, the peripheral task showed that AP's scaling abilities are extremely limited. Specifically, the scaling

behaviour shown at midline with her left hand was completely lost when objects were moved into her visual periphery, and she was unable to scale to objects at any location with her right hand. Her kinematic data further indicated failures in proper visuomotor functioning, as she showed deviations from controls with both her left and right hands. With her dominant, left hand, AP showed a generally slower peak velocity and longer overall movement time than controls, particularly for contralateral reaches. This pattern was even more evident with her non-dominant, right hand, where she showed slower velocities, longer movement times, longer times to MGA, and longer times to peak velocity across almost all target-positions. It is clear from these results that AP demonstrates severe motor and/or visuomotor difficulties with both hands.

In addition to AP's troubles with scaling and overall reach kinematics, her reach paths also showed a departure from those of controls under a number of conditions. In particular, with her right hand, AP tended to overshoot the object to its right side, before cutting sharply back to finish the grasp. This resulted in reach paths that show a 'hook' shape, rather than a smooth curve, especially for the midline and ipsilateral conditions. What's more, AP showed a reaching bias towards the point of fixation for contralateral reaches. Unlike SS, however, her reaching bias for ipsilateral reaches was away from the point of fixation. As a result, this behaviour seemed more akin to that of controls, in that the curvature of her reach paths was biased towards the hand being used. Although AP's path curvatures did not provide conclusive evidence for the presence of magnetic misreaching, further analysis revealed that eight (13%) of AP's peripheral grasps passed within 3cm of the fixation point. Furthermore, the kinematics of these reaches revealed that wrist height and velocity decreased as AP's hand entered the ROI in four of the eight trials. In a similar manner to SS, AP's fingers occasionally touched the table during these aberrant reaches, as if she was executing a grasp to the fixation point itself rather

than the peripheral target. Again, this is strong evidence for the presence of magnetic misreaching.

Conclusion. Study III sought to explore the abilities of patients with PCA to reach out and pick up objects in their periphery with both their dominant and non-dominant hands. Control subjects demonstrated an aptitude for precise grasping with either hand to objects located both at midline and in their periphery, though contralateral grasps proved slightly more challenging. RB's poor performance on the peripheral task mirrored that seen in Study I, as she showed impaired visuomotor functioning for objects positioned both at midline and in her visual periphery. MTB demonstrated a great deal of difficulty with this task, being unable to even initiate grasps to peripheral targets. This observation, combined with her poor visuomotor performance in Studies I & II, suggests that MTB suffers from severe optic ataxia. Evidence of SS's visuomotor dysfunction was very apparent in this Study, as he failed to scale his grasps to objects at any position with his dominant hand. In fact, SS's performance was far better on this task with his non-dominant, left hand. AP also demonstrated evidence of optic ataxia, as she was able to scale her grip for objects at midline with her dominant hand, but not for those in the periphery. AP also showed severe visuomotor dysfunction with her non-dominant, right hand. Finally, SS and AP both exhibited magnetic misreaching when attempting to grasp peripheral targets, especially those located contralaterally to the hand being used. This is the first time that such behaviour has been documented in patients with PCA, having been previously reported in patients with optic ataxia.

RB, SS, and AP all demonstrated excessively curved reach paths, both at midline and in the periphery, indicative of impairment in the transport phase of a reach. This behaviour introduces the possibility that these "inefficient" reaches could contribute to poor grasp site

selection in Study II. It could be the case that patients are able to properly select stable grasp sites on the objects during programming, but are unable to execute accurate enough movements to guide their fingers to those precise locations. This impairment could be a result of a loss of the fine motor control required to accurately coordinate finger movements, or an issue with arm coordination during the transport phase of the reach. However, results from Studies I and II challenge these possibilities. First, MTB and AP, who produced unstable grasps in Study II, both showed preserved fine motor control in their ability to accurately scale their grasps to the size of the target object in Study I. Second, RB and SS, who produced stable grasps in Study II, demonstrated reach paths indicative of deficits in the transport phase of arm movement. Therefore, we have little evidence to suggest that the poor visuomotor performance demonstrated by MTB and AP in Study II was a result of deficits in fine motor control or in proximal arm movements, rather than impaired contour analysis and grasp site selection.

General Discussion

Patients suffering from Posterior Cortical Atrophy are routinely diagnosed as suffering from one of a myriad of other disorders, such as homonymous hemianopsia, alexia, Alzheimer's disease, and optic ataxia, just to name a few. More recently, efforts have been made to define the clinical syndrome that is PCA. As a result, researchers and clinicians are beginning to understand the unique spectrum of deficits that can arise as a result of this progressive degenerative disease. This work is resulting in both an increased public awareness of PCA (e.g. Pratchett, 2008), and the growing acceptance that PCA may be a far more common affliction than was previously suspected. In response, research is now starting to focus more intently on the precise manifestation of PCA symptoms in a concerted effort to understand and further define this complex disorder. The current study sought to contribute to this important body of

work by performing a targeted investigation of the visuomotor and perceptual abilities of a small group of PCA patients.

Four patients were recruited along with healthy age-matched controls. Basic testing confirmed that all of our patients satisfied published criteria for the diagnosis of PCA, exhibiting a combination of alexia, agraphia, visual agnosia, environmental disorientation, simultanagnosia, and optic ataxia. Additionally, all patients showed relatively preserved memory, judgement, and insight into their disorder. The current study revealed that our patient group demonstrated deficits in reaching and grasping movements for visual objects under foveal and peripheral vision. These impairments showed no improvement when vision was obscured or when reaches were performed after a delay. Some patients were able to accurately select stable grasp sites on complex asymmetrical objects despite being completely unable to compare these same objects based on their shape. Below, the results of this experiment are evaluated in relation to current theories regarding the processing of visual information in the human brain. Additionally, the contribution of the current investigation to our understanding of PCA is discussed.

Visuomotor disturbances in Posterior Cortical Atrophy

Visuomotor malfunction has been a key feature of Posterior Cortical Atrophy ever since Benson's (1998) initial description of the disorder; all five of Benson's patients demonstrated some form of optic ataxia or misreaching. Since then, disturbances in visuomotor functioning have frequently been reported in cases of PCA (Caine, 2004), and optic ataxia has been suggested as a supporting feature for diagnosis with the disorder (Tang-Wai et al., 2004). However, a review of the literature reveals that a quantitative investigation into visuomotor functioning in patients with PCA has never been performed. Instead, the presence of optic

ataxia in cases of PCA has predominantly been identified based on *qualitative* observations of misreaching (e.g. Goethals & Santens, 2001; Mendez et al., 2002). One of the main goals of this study was to perform a detailed *quantitative* analysis of the grasping abilities of a small group of patients with PCA. More specifically, we sought to discover whether patients with PCA show similar kinematic behaviour to that which has been previously described in patients with optic ataxia.

All four patients in the current study met the generally recognised criteria for optic ataxia: inaccuracy when reaching or grasping visual objects that is not caused by visual field defects, impaired proprioception, intrinsic motor or oculomotor deficits, or cerebellar dysfunction (Rossetti, Pisella, & Vighetto, 2003). Previous research has shown that patients with optic ataxia demonstrate abnormalities in both the proximal and distal components of a reach (Jakobson et al., 1991). That is, they show deficits in the transport of the arm as well as the formation of a grasp. The current study revealed that PCA patients show a similar pattern of behaviour. In Study III, three of the PCA patients showed excessively curved reach trajectories compared to controls, indicative of inefficient reach strategies, while the fourth was unable to even initiate reaches to peripheral targets. Two patients demonstrated further evidence of a breakdown in the transport component of their reaches, as they missed the target block completely on a disproportionate number of trials. Similarly, deficits were seen in the grasp component of patients' movements, as patients demonstrated difficulties scaling their grip to the size of target objects and difficulty selecting stable grasp sites on asymmetrical shapes.

The proximal and distal components of a reach are coded independently at multiple levels of the nervous system. Proximal arm movements are controlled by bilateral vestibulospinal tracts, while distal grasping movements are controlled by projections from

contralateral corticospinal tracts (Brinkman & Kuypers, 1973). This segregation of control systems for reaching and grasping is maintained at the cortical level. Gallese, Murata, Kaseda, Niki, and Sakata (1994) found that transient inactivation of area AIP produced deficits in hand shaping, while inactivation of a slightly more caudal site produced misreaching. Furthermore, lesions to posterior parietal cortex have been documented that result in impaired grasp control with intact reaching (Jeannerod, Decety, & Michel, 1994). More recent research supports these findings, as the application of TMS to human aIPS has been shown to affect the kinematics of the grasp but not the reach (Rice, Tunik, & Grafton, 2006; Tunik et al., 2005). In spite of this parallel processing, the neural control centers for reaching and grasping are located in very close proximity, and the two processes are tightly linked. For example, increasing the size of a target object necessitates the production of larger maximum grip apertures, but it also produces faster wrist velocities (Bootsma, Marteniuk, MacKenzie, & Zaal, 1994). Likewise, increasing the distance to a target object necessitates changes in reach kinematics, but also produces larger grip sizes (Chieffi & Gentilucci, 1993). Furthermore, the timing of reach and grasp kinematics are tightly coupled and highly stereotyped. For example, maximum grip aperture always follows peak deceleration of the wrist, even when reaching movements have to be corrected due to perturbation of the target (Paulignan, MacKenzie, Marteniuk, & Jeannerod, 1991).

Based on these observations, it has been proposed that a central synchronisation system exists to temporally align the two components of a grasp (Jeannerod, 1986). However, because extrinsic and intrinsic object properties can alter both the transport and grasp components of a reach, Jakobson and Goodale (1991) suggest that the coordination of reaching and grasping goes beyond a simple temporal coupling. Instead, they propose that the posterior parietal cortex houses a higher-order control system for guiding prehension. These investigations offer a number of possible explanations as to why damage to PPC frequently

affects both the proximal and distal components of reach-to-grasp movements. First, the close cortical proximity of the reach and grasp control centers means that damage to the IPS frequently affects both systems simultaneously. Second, damage to higher-order control systems in the PPC would have a negative impact of both the proximal and distal components of prehensile movements. Finally, Jeannerod, Paulignan, and Weiss (1998) posit that the coding of the reach and grasp components of a movement does not run in parallel. Instead, they suggest that the information used to coordinate the two main components of a reach might flow in a serial fashion from transport to grip. They put forward this theory as an explanation for why there seem to be no examples of posterior parietal lesions affecting the reach without altering the grasp. Indeed, the results of the current study support these hypotheses, as none of the patients showed impaired grip scaling without concomitant reaching deficits.

Another hallmark of optic ataxia is that visuomotor deficits are frequently restricted to actions performed in peripheral vision, with intact functioning for reaches performed under foveal guidance (e.g. Milner et al., 1999a). The patients in the current study showed a trend towards a similar pattern of behaviour, but the dissociation was not complete. MTB and AP demonstrated appropriate scaling behaviour with their dominant hands for objects they were allowed to fixate, but this ability was lost when objects were presented in their visual peripheries. Conversely, RB and SS exhibited deficits in scaling behaviour for objects in central vision as well as in their peripheries. Specifically, when allowed to foveate objects, RB showed a complete absence of grip scaling, while SS's scaling behaviour was inconsistent and weaker than that of controls. Though MTB and AP demonstrated accurate grip scaling to objects under central vision, their reaches were not normal; both individuals exhibited long, protracted movements, and MTB's reach velocities were significantly lower than controls. This behaviour is not unusual, and has been reported previously for patients with optic ataxia. For example,

Jakobson et al. (1991) recorded reach-to-grasp movements from a patient with optic ataxia resulting from bilateral lesions in posterior parietal cortex. This patient exhibited lower peak velocities, longer movement durations, and longer times to MGA than controls for grasps made with visual feedback. Rossetti and colleagues (2003) suggest that slowing down movements may be an attempt to compensate for damaged on-line control centers in the parietal cortex by engaging slower visual feedback loops that can refine the programming of movements based on incoming visual information.

Some patients with optic ataxia have been observed demonstrating a behaviour termed 'magnetic misreaching' (Carey et al., 1997; Jackson et al., 2005), in which patients show a pathological reaching bias towards the point of fixation when directing an action to a peripheral target. The current study revealed evidence in favour of the presence of magnetic misreaching in two of our patients with PCA. Specifically, SS and AP both executed reaches that demonstrated kinematics resembling a reach directed towards the fixation point itself, rather than towards the peripheral target. Jackson and colleagues (2005) have suggested that this behaviour occurs when the visuomotor systems underlying eye and limb movements are not properly uncoupled in order to allow for each system to perform simultaneously independent actions. Indeed, eye and hand movements are known to be highly coordinated processes (Fisk & Goodale, 1985), as demonstrated by the tight temporal and spatial coupling seen between gaze fixation and grasp site locations (e.g. Desanghere & Marotta, 2011). In fact, the control of reaching under visual guidance is so 'primal' that it is thought to be controlled, in part, by subcortical structures, including the superior colliculus (Milner et al., 2003). Additional coordination and synchronisation is governed by key regions of posterior parietal cortex, such as 7m and V6a, which are known to respond to both eye and hand movements (Caminiti et al., 1996; Ferraina et al., 1997). In fact, the majority of 'reaching cells' in V6a have been found to

code activity in both retinal and spatial coordinates (Marzocchi et al., 2008). Similar results have been found for parietal regions LIP and MIP, which preferentially code eye movements and reaching movements, respectively. Despite controlling the action of very different effector systems, cells in both of these areas encode their actions using a continuum between eye- and head-centered reference frames (Mullette-Gillman et al., 2005). What's more, 'reach' neurons in MIP have been shown to update their target-related activity following a saccade during delayed grasping tasks (Batista & Andersen, 2001).

The robust cooperation between eye movements and hand guidance underlies our ability to quickly and accurately interact with objects around us. In fact, these processes are so intimately connected that it can be difficult to dissociate them behaviourally. Of course, the dissociation between eye and hand movements is not only possible, but necessary, for efficient and versatile object-interaction. Independent control of these two processes underlies our ability to execute a reach without direct visual guidance, or to shift our gaze away from an ongoing manual task. It is thought that the uncoupling of gaze and prehension relies on cortical systems that send inhibitory signals to midbrain structures (Milner et al., 2003), such as the superior colliculus, and recent studies have identified the parietal-occipital junction as a potential source of this inhibition (Clavagnier, Prado, Kennedy, & Perenin, 2007). When these cortical regions are damaged, as is seen in cases of optic ataxia, individuals can be left without the ability to uncouple their eye and hand movements. Milner and colleagues (2003) suggest that magnetic misreaching therefore represents a 'primitive' form of reaching, in which cortical inhibition of midbrain structures is lost. In the current study, SS and AP demonstrated evidence of this behaviour, making reaches in which they physically attempted to grasp the fixation point despite being directed to reach for a target object located in their periphery. Furthermore, the fact that all four patients showed great difficulty suppressing the urge to look at the object to

which they were directing their reach, demonstrates their inability to inhibit the powerful coordination of eye and hand movements.

Vision for perception and vision for action: Parallel streams of visual processing

In 2001, Milner and colleagues presented patient IG who demonstrated optic ataxia as a result of extensive bilateral posterior parietal lesions. IG showed what the authors referred to as a "paradoxical improvement" in grasping following a delay. Specifically, IG demonstrated no grip scaling when reaching to peripheral targets under visual guidance, but appropriate grip scaling during delayed real grasping and delayed pantomime grasping. The authors suggest that IG's improved performance was made possible thanks to the recruitment of an alternate visual processing pathway during the delayed tasks. Specifically, Goodale and Milner (2004) contend that the ventral visual stream – specialised for processing longer lasting visual information – guides reaches in the absence of immediate visual feedback. In the present study, patient RB was the only individual to show a complete absence of grip scaling for grasps made in unrestricted viewing conditions. Unlike IG, RB did not show the same paradoxical behavioural improvement following a delay. In fact, all of the PCA patients who were able to scale their grasps to the size of objects under visual guidance showed much poorer performance on a reach-to-grasp task following a delay. However, this result is hardly surprising given the fact that all four of the patients exhibited perceptual deficits indicative of ventral stream damage.

The timing of a switch in visuomotor control from the dorsal to the ventral stream following visual occlusion is not entirely clear. Although Goodale, Westwood, and Milner (2004) proposed that the switch in control occurs immediately upon visual occlusion of the target, others have found evidence for a more progressive change in performance depending on the length of the delay (Bradshaw and Watt, 2002; Himmelbach and Karnath, 2005). These findings

suggest a more gradual shift from dorsal to ventral control, and the results of Study I support this conclusion. MTB, SS, and AP all showed evidence of scaling behaviour with visual feedback readily available. When reaches were performed immediately following visual occlusion, SS and AP still showed scaling, while MTB's ability to scale her grip to the size of the block disappeared. It wasn't until a three second delay was imposed between object viewing and movement onset that all three patients showed no scaling behaviour. As such, there seemed to be a progressive disappearance of scaling ability as the length of the delay increased.

MTB, SS, and AP demonstrated behaviour more akin to another patient studied by Milner and colleagues: DF. As described earlier, DF suffers from visual object agnosia resulting from lesions confined to inferotemporal cortex. In contrast to IG, DF shows perfect grip scaling under visual guidance but loses this ability following a delay. Milner and colleagues propose that this behaviour occurs as a result of DF's perceptual system being unable to form a visual percept of the target object, thereby depriving her visuomotor system of an accurate object representation on which to program a precise grasp following the removal of immediate visual information. The current study suggests that a similar behaviour is seen in PCA patients who suffer from extensive loss to visual processing areas in the ventral visual stream.

The observation that visuomotor functioning is often spared for central vision despite bilateral destruction of posterior parietal cortex has added to the heated debate regarding the roles and organisation of the two visual processing streams (e.g. Milner & Goodale, 2008; Pisella, Binkofski, Lasek, Toni, & Rossetti, 2006). Some authors have presented this behaviour as evidence that the dorsal stream's control of action is restricted to movements performed in peripheral vision (Rossetti et al., 2003). This leads to the argument that the division of labour for perception and action between the ventral and dorsal streams is not as clear cut as Goodale and

Milner's theory suggests, and that the ventral stream actually plays an important role in the control of action. Milner and Goodale (2008) defend their position by citing evidence that the ventral stream places a huge amount of emphasis on the highly-detailed information provided by the fovea, resulting in a great deal of cortical magnification for central vision. Meanwhile, in the dorsal stream, information from the periphery is just as important as that coming from central vision, resulting in very little cortical magnification. As a result, when the dorsal stream is compromised due to parietal lobe damage, the ventral stream is far better equipped to take over visuomotor responsibilities for actions performed under central vision (Milner & Goodale, 2008). Ultimately, both parties agree that the central sparing seen in optic ataxia is likely a result of slower, perceptual systems taking over for damaged action-specialised centers in the dorsal stream. Observations from the current study support this conclusion, as three of four patients showed a far greater preservation of visuomotor abilities in central vision compared to peripheral vision. Additionally, the general slowing and protraction of movements seems to concur with the idea that slower, perceptual systems are compensating for impaired dorsal functioning.

Beyond vision: the role of somatosensation in reaching

The current investigation has focussed heavily on the impact of parietal damage on reaching and grasping with regards to visuomotor dysfunction. However, it is also important to address the role of the parietal cortex in the processing of other sensory modalities, specifically somatosensation, which includes tactile and proprioceptive signals. Strategically positioned between the primary visual and primary somatosensory cortices, parietal association areas play an important role in the integration of these two modalities (Grefkes, Weiss, Zilles, & Fink, 2002; Longo, Musil, & Haggard, 2011). Accordingly, both vision and proprioception provide important

information for the programming and execution of reaching and grasping movements (Medendorp, Goltz, Crawford, & Vilis, 2005). However, the relative contribution of these two modalities is still being debated. For example, it has been shown that haptics provide substantially less precise information than vision for motor programming, and grasping performance made using congruent haptic and visual information regarding object size is no different from that using vision alone (Pettypiece, Goodale, & Culham, 2010). It would seem, then, that vision is a far more important source of information for motor programming than somatosensation. However, when there is a discrepancy between tactile and visual cues, or when vision is less reliable, the influence of haptics becomes far more apparent. For example, when vision is limited, such as during a peripheral grasping task, proprioceptive information has been shown to improve reach precision even when continuous visual feedback is available (Monaco et al., 2009). Furthermore, on-line error adjustments can occur without vision of the hand, even when the target is only defined by proprioceptive cues (Gosselin-Kessiby, Messier, & Kalaska, 2008). Clearly, then, proprioception plays an important role in the guidance of reaching and grasping actions. Indeed, certain reach-dominant regions of posterior parietal cortex have been found to primarily receive proprioceptive information (Filimon, Nelson, Huang, & Sereno, 2009).

Given the importance of posterior parietal cortex in the processing and integration of visual and somatosensory information, it is not surprising that damage to this area can cause both visuomotor and 'proprioceptivo-motor' impairments (Blangero et al., 2007). Once again, however, studies looking at patients with parietal damage have produced mixed conclusions regarding the importance of proprioceptive input for reaching and grasping. For example, recent investigations have shown that patients with substantial proprioceptive loss are still able to reach accurately to visualised targets both with and without vision of their hand (Coslett,

Buxbaum, & Schwoebel, 2008). With regards to optic ataxia, many studies, including the formative work of Perenin and Vighetto (1988), have reported the absence of somatosensory deficits. For this reason, optic ataxia is most commonly defined as a specific deficit of spatial-motor transformations when using *visual* information. However, recent investigations have revealed that some patients with optic ataxia demonstrate large reaching mislocalisations when reaching for proprioceptive targets without visual feedback (Blangero et al., 2007), suggesting that motor deficits in optic ataxia are not limited to visual targets.

In light of these recent findings, it is important to consider the possibility that damaged proprioceptive systems may have played a role in some of the behaviours exhibited by our patients. As we have already seen, proprioceptive feedback is more heavily relied upon during conditions in which visual information is absent or less accurate, such as open-loop or peripheral grasping – conditions in which we saw a decrease in reaching accuracy across our patient group. It is possible that this behaviour was a result of an impaired ability to accurately monitor proprioceptive feedback cues and to guide correct ongoing movements based on this information. For example, without online visual feedback of a reach, we are completely reliant on proprioceptive feedback to monitor the movement and location of our arm. This information must then be compared with an internal representation of the immediate environment, as well as the previously generated motor-plan, in order to determine whether the reach is proceeding accurately or whether movement corrections are required. Within the confines of the current study, it is very difficult to determine whether a similar malfunction in proprioceptive processing was affecting patient performance, since decreases in reaching accuracy would already be expected in the peripheral and open-loop conditions as a result of our patients' readily apparent visuomotor and perceptual impairments. For example, the most obvious explanation for the drop in accuracy seen in the patient group during open-loop grasping is they lack an accurate

visual percept or memory of the target on which to program their reaches, resulting in a dramatic drop in grasp precision regardless of somatosensory integrity. However, given the recent evidence demonstrating proprioceptive dysfunction in optic ataxia (Blangero et al., 2007), it is possible that our patients' performance was affected by damage to both visual and somatosensory systems.

Ventral versus dorsal dysfunction: Subtypes of Posterior Cortical Atrophy?

After performing an extensive literature review, Caine (2004) concluded that PCA is characterised by a core visuospatial deficit due to occipitoparietal atrophy, and she suggests that occipitotemporal symptoms are infrequent. She argues that the majority of seemingly ventral-based symptoms seen in PCA, such as impaired object recognition, are actually secondary consequences of dorsally-based deficits, such as dorsal simultanagnosia (Della Sala, Spinnler, & Trivelli, 1996) or a restricted attentional field size (Stark, Grafman, & Fertig, 1997). Despite these contentions, cases of probable ventral subtypes of PCA have been recorded. For example, Hof and Bouras (1991) presented a patient whose primary symptom was visual object agnosia. Importantly, a neurological comparison revealed that this patient showed more extensive atrophy in primary visual and temporal association areas than patients with typical Alzheimer's disease, but less prominent atrophy in posterior parietal cortex.

None of the patients in the current study demonstrated symptomology indicative of a purely ventral or a purely dorsal subtype of PCA. However, despite the highly mixed symptomology presented by our patients at the time of testing, their histories tell a slightly different story. For example, RB initially presented to her neurologists with only perceptual complaints, while MTB suffered from primarily visuomotor problems. Given the length of time these individuals have been experiencing symptoms, it is perhaps not surprising that they all

now exhibit more of a mixed disorder. Therefore, our research shows no evidence for the presence of purely ventral or dorsal subtypes of PCA in a small group of patients, but suggests that individual patients may experience primarily ventral of dorsal symptoms early on in the disease. As such, a ventral/dorsal subclassification of PCA may be useful in identifying the primary site of atrophy early on in PCA, but seems to become less valuable as the disease inevitably progresses to a state of more diffuse cell loss.

PCA: Clinical observations

Although each of the patients in our study exhibited subtle differences in their abilities and deficits, there were clear behavioural similarities across the patient group. All four PCA patients were cognitively normal as measured by the MMSE, but demonstrated mild to moderate impairment on the DRS-2. However, scores on the DRS-2 were a result of poor performance on the Attention subtest, which requires subjects to identify target numbers embedded in an array, and the Construction subtest, which requires subjects to copy visual designs. It seems that the 'impairments' being detected by the DRS-2 were primarily driven by deficits in visual perception and graphomotor reproduction. This observation highlights the importance of taking into consideration the impact of pervasive visual impairments in PCA when interpreting and reporting scores on tests that are designed to measure 'general cognitive functioning'. In fact, this warning also extends to other commonly administered tests, such as those used to examine attention, spatial awareness, basic visual functioning, or memory. Any such test that requires the recognition of letters, symbols, or designs is vulnerable to false conclusions and misinterpretation when used to test patients with PCA.

The patients reported here unanimously demonstrated slowed reaction times compared to controls, and two of the four patients also showed slowed rates of repetitive finger tapping.

Reaction times are well known to decrease with age, and it has been found that speed is highly correlated with performance on various cognitive measures (e.g. Salthouse, 1994). However, there is still no general consensus as to the cause of such changes. Multiple theories have been put forward, such as reduced dendritic branching, a decreased number of active synapses, or a loss of myelin in the aged brain. Another speculation is that age-related slowing may arise due to diffuse cell loss, which forces neural signals to take more circuitous pathways between cortical sites (Salthouse, 2000). This suggestion is particularly intriguing in the context of the current study: if generalised cell loss is the cause of elongated reaction times in healthy aged populations, then it follows that more extensive cell loss resulting from PCA – especially in visuomotor pathways – could result in an even greater degradation of simple reaction time. Recent studies have suggested that simple reaction times may increase with age due to individuals adopting a more conservative response criterion (Godefroy, Roussel, Despretz, Quaglino, & Boucart, 2010). These authors show that older participants require a higher level of evidence that the target signal had been presented before they will trigger a motor response. Given that patients with PCA exhibit extensive deficits in visual perception, it seems reasonable to conclude that they may adopt a more conservative response strategy than healthy aged participants. In other words, if patients with PCA have learned to be skeptical of the information they receive from their perceptual system, they may delay even longer than controls before making a motor response in order to 'verify' what their visual system is telling them. Godefroy and colleagues (2010) are quick to point out that response strategies do not explain all of the variation in reaction times, and that slowed perceptual and motor processes are also important determinants of response slowing. Given the decreased rates of finger tapping exhibited by some of our patients, it seems that basic motor slowing is also a factor in these tests.

On multiple occasions, RB has reported generalised colour disturbances, such as perceiving the walls of a room as a different shade or seeing colours in a black and white image. Josephs and colleagues (2006) reported that visual hallucinations occur in up to 25% of patients with PCA. In a large-group study, Josephs et al. found that PCA patients with hallucinations show greater atrophy in primary visual cortex, thalamus, and basal ganglia than PCA patients without hallucinations. Based on these findings, the authors suggest that hallucinations are likely a result of the destruction of thalamocortical and ascending midbrain pathways, rather than atrophy in posterior association cortices. It should be noted, however, that RB's hallucinations are transient, colour-based visual disturbances, whereas the patients in Joseph et al.'s study report "well formed, recurrent, spontaneous, and nonfleeting" distortions, which are dominated by visions of people, animals, and insects. Furthermore, these patients exhibit parkinsonism and rapid eye movement sleep behaviour disorder – characterised by wild flailing movements occurring during sleep. Such symptoms have not been reported in RB's case. Therefore, another explanation for RB's hallucinations seems necessary. Santhouse, Howard, and ffytche (2000) observed an association between colour hallucinations and age-related macular degeneration, which RB exhibits to a mild extent. Santhouse and colleagues suggest that these hallucinations are a result of "selective de-afferentation with localised hyper-excitability within the colour area [of the brain]." This theory comes from two observations: first, cellular degeneration was found throughout the ventral colour pathway in a patient with macular degeneration (Clarke, 1994); second, area V4, which specialises in colour processing, was found to be tonically hyperactive in patients with macular degeneration who experience colour hallucinations (ffytche et al., 1998). Given that RB's hallucinations are restricted to colour disturbances, it seems more likely that her colour perturbations are a result of atrophy and hyper-excitability in colour processing areas of her cortex, rather than damage to midbrain structures. Interestingly, since this study was

performed, MTB has also begun to report colour disturbances similar to those experienced by RB.

All four patients in the current study demonstrated symptoms indicative of simultanagnosia. Simultanagnosia is a rare neuropsychological disorder, characterised by an inability to attend to or perceive more than one element of an object or a scene simultaneously. It most commonly occurs as part of Balint's syndrome due to bilateral occipito-parietal damage, but it can also result from damage to occipito-temporal areas (Chechlacz et al., 2011). For this reason, it has been suggested that simultanagnosia may exist as two distinct subtypes – ventral and dorsal – depending on the location of cortical damage (Farah, 2004). These variants differ in their clinical presentation: dorsal simultanagnosia is characterised by the detection and perception of only one visual element at a time, while ventral simultanagnosia is characterised by the restriction of recognition to a single object at a time, despite the ability to detect multiple stimuli. Our patients all made errors on a basic object counting task, which is a strong indicator of an impairment in perceiving or attending to multiple objects simultaneously. More specifically, this behaviour reflects a dorsal symptomology, given that patients with ventral simultanagnosia are able to count scattered dots (Kinsbourne & Warrington, 1962).

Considering the multitude of higher-level visual deficits seen in PCA, the specific effect of simultanagnosia can often be difficult to observe. For example, it can be very challenging to dissociate simultanagnosia from other deficits such as visual object agnosia, neglect, or alexia. However, a number of observations point to the presence of simultanagnosia in the current study. One example of the difference in performance between the ATT subtest of the DRS-2 and the Benton Visual Form Discrimination task (VFDT). All four PCA patients showed a relatively preserved ability to match visual designs on the ATT subtest, but were unanimously impaired on

the Benton VFDT. What's interesting is that these tasks are almost identical, save a few key differences. In both tasks, participants are shown a visual design, such as shapes or patterns, and are required to locate that same design on a test page containing four similar designs. There are, however, a couple of key differences between these two tasks that potentially explain this difference in responding. Firstly, the designs on the ATT subtest contain geometrically distinct elements, such as acute angles versus smooth curves, whereas the differences between the designs on the Benton VFDT are more subtle alterations in shape or orientation. Secondly, each design in the Benton VFDT actually consists of three individual shapes, whereas each design on the ATT subtest contains a single 'object' constructed from one continuous line. The most obvious explanation for the observed difference in accuracy between the two tests is that the ATT subtest is simply easier. While this possibility likely holds credence, two other explanations are interesting to consider with regards to the influence of simultanagnosia. Firstly, simultanagnosics are known to use a featural – parts-based – approach to identify objects, focussing their analysis of a figure on a single aspect or element of the overall design. Specifically, they will attempt to identify objects by extrapolating the information they receive from a single feature. The presence of distinctive features between designs on the ATT subtest would therefore enable patients with simultanagnosia to make successful comparisons even if they were unable to perceive the entire object as a whole. Secondly, the fact that the designs on the Benton VFDT contain multiple objects whereas the ATT subtest contains only single designs suggests that patients with simultanagnosia would struggle more on the Benton VFDT due to the sheer number of objects that need to be processed at once. This explanation has its weaknesses, however. For one, despite using only single objects as stimuli, the ATT subtest still requires participants to locate the target object from amongst an array of distractors. It seems that someone with simultanagnosia would be unable to complete this task, however simple the

stimuli. Ultimately, it is most likely that test difficulty, simultanagnosia, and visual form agnosia all contributed to the disparity in performance between the ATT subtest and the Benton VFDT.

A stronger case can be made for the presence of simultanagnosia by considering patient AP individually. AP's perceptual deficits were far less pronounced than the other three patients, as her ability to identify objects and faces was intact, whereas RB, MTB, and SS all showed moderate to severe impairments on these tasks. However, like the rest of the patient group, AP showed great difficulty on the Benton Line Orientation Task and the Benton VFDT. An important shared characteristic of these two tests is the presentation of a large number of stimuli all at once. Based on these results, it seems that the relative preservation of AP's perceptual abilities is dependent on the number of objects present. In support of this conclusion is AP's performance on the shape matching tasks in Study II. Her ability to correctly match objects based on their shape was significantly worse than controls for the tabletop task, in which two blocks were presented together. However, her performance on the computer based task, in which the two shapes to be compared were presented one at a time, was no different than controls. What's more, AP was also the only patient whose performance was better on the computer based task than the tabletop task. This represents a rather clear indication that AP's perceptual deficits are a result of an inability to visually analyse more than one object at a time.

A common theme among patients with PCA is the complaint that visual stimuli, especially printed words and images, 'jump' and move around on the page, making identification impossible. The preservation of insight and judgement late into the disease means that these visual disturbances are particularly frustrating. The following is MTB's description of her experience with the Benton VFDT:

> Rationally, I can understand [how to perform the task], but I can't see it. There's just too much. There are too many lines. It's all moving. I just can't [do it]. Mostly because it looks like things are swimming in the background. I can see curves and something that looks like an oval (as she points to a circle), and a box (as she points to a square), and this (as she points to a triangle) – I don't know what this is. Once I look away, it's gone. I can't hold the memory in my head to say that this is the same as that. These coils (pointing to the plastic coils of the testing booklet) are in the way, and there are just too many distractions. You know when there's going to be a big storm, and the clouds are roiling? It looks like that – the background. I can't focus on anything. It's frustrating! [Doctors] always give me these diagrams with lines going everywhere, and for me it's never static. My eyes can't chase the lines.

On another occasion, MTB described the trouble she had experienced upon entering a large atrium in a government building. The floor was elaborately laid, made up of alternating white and black hexagonal tiles. MTB stopped dead in her tracks. To her, each tile appeared to be a different height, as if the entire room were an uneven staircase. She watched as her husband walked effortlessly across the floor to the middle of the room, but she could not follow. MTB described a fierce argument taking place inside her mind. On the one hand, she *knew* that the floor was flat – her husband had just proven as much. On the other hand, her perceptual system insisted that the tiles were uneven, and that she would surely trip if she were to attempt to cross. This anecdote illustrates the struggle that patients with PCA face on a daily basis. With progressively failing perceptual and visuomotor systems, individuals with PCA are forced to constantly re-evaluate and override the faulty information being sent to them. Life becomes like a complex visual illusion, where every moment requires a concerted effort to extract the hidden reality from the noise.

Future directions

The current study revealed that patients with PCA exhibit many of the same behaviours that have previously been reported in patients who suffer from optic ataxia due to more localised lesions. It would be interesting to continue this line of investigation by adapting the current experiments to investigate additional known features of optic ataxia. For instance, patients with optic ataxia have been shown to demonstrate severe deficits in the on-line correction of visually guided movements; Gréa and colleagues (2002) showed that one individual, patient IG, was unable to alter the trajectory of an ongoing reach when the target object was displaced at the start of a pointing or grasping movement. Instead, IG would complete her initially programmed reach and then execute a secondary movement to the new object location. Another interesting adaptation of the current experiments would be to investigate the ability of PCA patients to avoid obstacles in their workspace. Previous work has shown that patients with bilateral dorsal stream damage fail to take into account the location of obstacles when required to reach between them, but they can accurately indicate the mid-point between the same objects in a bisection task (Schindler et al., 2004). Interestingly, the opposite pattern has been observed in patients with bilateral ventral-stream damage (Rice et al., 2006), once again providing a double-dissociation between ventral and dorsal systems for perception and action, respectively. Rice and colleagues (2008) have further investigated obstacle avoidance, showing that patient MH, who suffers from unilateral optic ataxia, demonstrated improved obstacle avoidance following a delay.

The current study revealed a number of intriguing observations regarding PCA symptoms that warrant further investigation. For example, poor performance on the shape matching task in Study II was shown to be a result of deficits in mental rotation. As far as we are

aware, impairments in mental rotation have not been previously reported in the PCA literature, so it would be interesting to further explore this symptom in a PCA population. The disturbances in colour perception reported by RB and MTB open up another potential path for future investigation. Although complex hallucinations in PCA were the focus of a detailed investigation by Josephs and colleagues (2006), transient colour hallucinations, like those reported here, have not been afforded the same level of attention. Given that two of our four patients experience colour disturbances, it is possible that this symptom is more common than has been previously reported.

Finally, PCA coupled with neuroimaging technology represents an excellent opportunity for us to learn more about the functionality of specific cortical areas; it would be highly valuable to perform a targeted investigation into the relationship between cortical losses and behavioural deficits in PCA. Given the subtle differences in symptom presentation between cases, PCA presents an opportunity to link individual deficits to cell loss in specific areas of the brain. An excellent example of this is the intriguing behavioural dissociation between grip scaling and grasp site selection seen in the current study. Specifically, RB was unable to scale her grasps to the size of target objects but could select stable grasp sites on asymmetrical shapes, whereas MTB showed normal grip scaling but poor grasp site selection. Such a dissociation represents an opportunity to learn more about the neural control of these two facets of visuomotor functioning. PCA also allows for a longitudinal study of the functional re-organisation of the brain following progressive cortical atrophy. For example, fMRI technology could be used to track changes in the pattern of brain activity for a visual task over an extended number of visits. By comparing the shifting activity map with the areas of cortex showing atrophy, much could be learned about how the brain progressively compensates for the gradual destruction of important cortical regions.

Conclusion

The studies presented in this thesis are the first to perform a quantitative analysis of the visuomotor deficits exhibited by patients with Posterior Cortical Atrophy. These experiments not only reveal that patients with PCA demonstrate similar kinematic behaviours to those seen in patients with optic ataxia, such as impaired grip scaling to peripheral targets, poor selection of stable grasp sites, and magnetic misreaching, but also that their visuomotor dysfunction includes problems not usually associated with optic ataxia, such as impaired kinematics for reaches made under central vision, and a loss of accurate grip scaling following a delay. Furthermore, the current investigation revealed neuropsychological abnormalities that have not been previously reported in PCA populations, such as impaired mental rotation and generalised colour distortions.

It is our belief that PCA is a more common affliction than is generally reported. One of the goals of the current research was to improve the general understanding of PCA symptomology, thereby helping clinicians to better identify and differentiate PCA from other medical conditions. Ultimately, we hope that this research will help expedite diagnosis, which would allow patients with PCA to receive the correct medical treatments earlier in the disease. Generating a better understanding of how PCA symptoms manifest themselves also helps physical and occupational therapists to better tailor their care programs when working with PCA patients, and facilitates the creation of coping strategies for patients and caregivers.

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