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Visual and non-visual control of movement: the role of proprioception in upper limb function after stroke

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PhD in Rehabilitation and Participation Science

Program in Occupational Therapy

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Visual and Non-Visual Control of Movement: The Role of Proprioception in Upper Limb Function After Stroke

by
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Abstract of The Dissertation

Visual and Non-Visual Control of Movement:

The Role of Proprioception in Upper Limb Function After Stroke

by
Nathan A. Baune

Doctor of Philosophy in Rehabilitation and Participation Science

Washington University in St Louis, 2021

Professor Benjamin A. Philip, Chair

This dissertation presents a series of studies into human reach and grasp, focusing on the neural systems and behaviors of upper-limb action that underly performance under varied sensory conditions: specifically, acting with and without visual feedback of the limb and under typical or impaired proprioceptive sensation (proprioceptive decline with aging and proprioceptive deficit following stroke). Under typical conditions, a combination of visual and non-visual (e.g., proprioception) sources of information are used to guide action. In the instance of stroke survivors or elderly individuals with proprioceptive deficits/decline, there may be a necessary reliance on visual information to perform. The studies are conducted in healthy adults (across the lifespan) and stroke survivors, who often suffer from somatosensory deficits. The overall goal of each study is: 1) the identification of neural systems involved in reaching and grasping *without* online visual feedback of the limb, 2) the development and validation of a novel approach to measuring upper-limb proprioceptive function, and 3) a pilot study using head-mounted VR to assess the relationship between proprioceptive capacity/deficit (healthy individuals and stroke survivors) and performance with or without online visual feedback of the limb during varied reaching tasks (ballistic reach vs slow/controlled reach).

Chapter 1: Introduction

1.1 Proprioception and the upper limb

The term “proprioception” was coined in the early 19th century and translates from Latin roughly as “to grasp one’s own”, such as to understand the position of our limbs relative to the body or the trajectory and velocity of a limb in motion (Evarts, 1981; Sherrington, 1907, 1909). Proprioception may be best thought of as a construct which collectively includes our sense of body position, movement, effort, force, and heaviness (Collins, Refshauge, & Gandevia, 2000; S C Gandevia & McCloskey, 1977; Simon C Gandevia, Refshauge, & Collins, 2002; Simon C. Gandevia, Refshauge, & Collins, 2002; Proske & Gandevia, 2012; John C Rothwell, 1987; J. L. Smith, Crawford, Proske, Taylor, & Gandevia, 2009; Stillman, 2002). The similarities and disparities between these proprioceptive modalities are not well understood. Relative to position and movement sense, our sense of effort, force, and heaviness are seldom addressed in the proprioception literature (Bertrand, Mercier, Shun, Bourbonnais, & Desrosiers, 2004; S C Gandevia & McCloskey, 1977; Lin et al., 2015).

Proprioception’s importance is most obvious, perhaps, in cases of total deafferentation (absence of incoming sensory signals). Case studies in patients who have suffered large fiber neuropathy and a selective loss of somatosensory afferents (without a loss to motor efference) show the drastic impact of deafferentation on motor control. In fact, without these afferent input’s patients cannot stand, walk, or manually interact with the world unless they rely entirely on visual feedback. These patients show exaggerated errors in reaching suggestive of reaching without intrinsic sensory feedback and while visual feedback can help them compensate, movement quickly degrades when vision is removed (Ghez, Gordon, & Ghilardi, 1995a; Gordon, Ghilardi, & Ghez, 1995a; J C Rothwell et al., 1982; R. L. Sainburg, Ghilardi, Poizner, & Ghez, 1995; Tuthill & Azim, 2018). Only through intensive re-training to act while relying on visual feedback are they able to regain some functional independence, and even then, their performance never reaches pre-injury levels.

The impact of proprioceptive deficits in stroke survivors and proprioceptive decline due to aging isn’t as immediately obvious (Adamo, Alexander, & Brown, 2009; Adamo, Martin, & Brown, 2007; Hughes, Tommasino, Budhota, & Campolo, 2015). In stroke survivors, the degree of proprioceptive deficit varies widely (Connell, Lincoln, & Radford, 2008); not to mention that research becomes complicated when motor performance can be impacted by a panoply of deficits. We can hypothesize how proprioceptive deficits or decline may affect performance and motor control based on existing research, though further research is needed to draw actionable conclusions.

1.1.1 Historical background of proprioception research

The term proprioception is believed to have been coined by the English neurophysiologist Charles Sherrington as early as 1906 (Evarts, 1981; Sherrington, 1907, 1909), though the idea of a sense responsible for perceiving the body had been championed and refuted for hundreds of years prior (Bell, 1833; Proske & Gandevia, 2012). Preceding evidence of proprioceptors (sensory receptors which contribute to our proprioceptive senses) and their role in proprioception, it was considered that such a sense was constructed entirely through our motor commands (Bell, 1833), which tend to have reliable effects on bodily position and motion. In other words, whenever we *willed* to move (as it was oft described at the time), that *will*/motor command gives rise to sensation of activity and movement. This was referred to as a “sensation of innervation”. In response, Sherrington and peers argued that we are still able to discern limb position when sitting still—when there are no motor commands or visual feedback. And so, there were two schools of thought: 1) body sense stems from central information, and 2) body sense stems from peripheral information (Proske & Gandevia, 2012).

Henry Charlton Bastian, who coined the term “kinesthesis”, was the first to consider a hybrid of central and peripheral factors (Bastian, 1887), though the proposed peripheral mechanisms were as opaque as previous accounts of central mechanisms. Impending discoveries by Sherrington and peers would lead to an upsurge in popularity of the “peripheral” school of thought; Bastian prematurely abandoned his hybrid theory in favor of peripheral mechanisms. Sherrington was the first to link sensory neurons that innervate proprioceptors to posture and movement control, albeit others had documented the sensory organs (proprioceptors) prior (Sherrington, 1907; Tuthill & Azim, 2018).

The prevailing focus in proprioceptive research throughout the early 20th century was on sensory afferents, and in fact the predominant hypothesis was that receptors in the joints played the largest role. Though not all abandoned the possibility of central mechanisms and it wasn’t long before there was evidence to support the role of central mechanisms in proprioception (Lashley, 1917).

1.1.2 Proprioception research in the present

It has been over a century since Sherrington’s earliest published work into proprioception, and over two centuries since his predecessors described a “sensation of innervation”, yet proprioception is still poorly understood, or at least, that is a perennial sentiment in the proprioception literature (Findlater & Dukelow, 2016; Proske & Gandevia, 2012; Tuthill & Azim, 2018). If it is poorly understood, it isn’t for a lack of trying. Proprioception has garnered attention from a wide range of scientific fields, in no small part due to its importance in motor control and motor learning.

Laudable basic and translative research has advanced our understanding of proprioception at a remarkable pace. However, the greatest attention has been paid to the lower limb, likely due to the increased risk of falls that accompany proprioceptive deficits. Yet, upper-limb function is crucial to most of the activity’s therapists retrain stroke survivors to perform; tasks that are typically relevant to functional independence.

We have a rudimentary understanding of the relevance of proprioception in enabling everyday activity. There is, however, growing evidence suggesting that “proprioception” significantly contributes to clinically meaningful outcomes. Proprioception is in quotes because the evidence is based upon diverse measures that assess different proprioceptive modalities to varying degrees of success. As will be discussed, it is questionable whether some measures properly reflect proprioceptive capacities most relevant to functional outcomes. It is unclear how proprioceptive modalities factor in and whether we might be able to meaningfully improve outcomes for individuals with proprioceptive deficits and decline through clinical intervention (Leeanne Carey, Macdonell, & Matyas, 2011; Findlater & Dukelow, 2016; Hughes et al., 2015; Park, Wolf, Blanton, Winstein, & Nichols-Larsen, 2008).

So why does our knowledge of proprioception, whether higher order processing and perception, or low-level circuitry, lag so far behind other sensory systems, such as olfaction, audition, and vision? There are numerous possible explanations, which I will address as we move through our discussion. Many of these explanations address possible limitations of existing proprioception research and directly informed the research presented in chapters 2-4.

1.1.3 Psychophysical concerns in proprioception research

> *"The subject of proprioception lies at the boundary between neurophysiology and neuropsychology" (Proske & Gandevia, 2012).*

While the sentiment of this quote could apply unequivocally to any realm of sensory and sensorimotor research, it is especially astute regarding our current (lack of) understanding of proprioception and the inherent difficulties of proprioceptive research. To "grasp one's own" requires a neural accounting of sensory afferents and central processes, including ongoing motor commands and the prediction of bodily outcomes. Discerning the streams of peripheral and central information contributing to our body state estimates is a matter of great interest to researchers across many fields of study. While early research in proprioception was predominately conducted by neurophysiologists, ongoing research ranges from experiments in neural circuits of insects to human neuroimaging to behavioral studies, cognitive science, and clinical research.

Part of what has made proprioception so difficult to study is that, unlike the eye, ear, or even tactile sensations, proprioceptive modalities are not easily attributable to one sensation. Proprioceptive sensation is also distributed throughout the body; there isn't a localized central organ such as an eye or nose. Both factors may attribute to the fact that we are largely unaware of proprioceptive sensations. Additionally, proprioceptive signals are predictable: our nervous system usually *knows* that movements are forthcoming and anticipate the somatosensory repercussions. The popular psychophysical explanation is that we most acutely "feel" the sensations which subvert expectations (Proske & Gandevia, 2012, 2018). Our awareness of proprioceptive sensations may have little bearing on the state of proprioceptive research, though it extends into an issue that likely does: proprioception as a perception versus sensation.

The potential disconnects between proprioceptive perception and the unconscious proprioceptive information actionable in motor planning and execution is a serious concern that researchers have little power to address. There is evidence, however, that proprioceptive information regarding limb configuration is available to plan reaching trajectories even when the same information isn't available to correct for limb drift, a phenomena which occurs when performing a repeated reaching task without vision (reach out to point A and back to point B)(Patterson, Brown, Wagstaff, & Sainburg, 2017). If accurate proprioceptive information is available to certain processes of motor planning and execution and not others, it seems plausible that a disconnect between perception and sensation may exist as well. Currently, we rely on subjective report (perceptions) to measure proprioceptive capacity/deficit. Though within these familiar constraints, there is significant work to be done.

1.1.4 Proprioceptors and other sensory afferents

Body state estimates, including estimates of limb position/configuration and movement, are formed through the input of numerous afferent sources. Vision can tell us where our limbs are in space. Tactile sensation may also be informative; for example, limb movement can be detected through skin deformation as we move, and finger position can be informed via the points of contact on an object. In mammals, the primary source of peripheral proprioceptive afference is a set of specialized sensory receptors: these proprioceptors include muscle spindles, Golgi tendon organs, and joint receptors.

Muscle spindles are embedded in mammalian skeletal muscles and provide brief bursts of action potentials with muscle stretch. Muscle spindles have been argued to play the largest role in position and movement sense (Proske & Gandevia, 2012). Their importance is demonstrated in humans by studies where vibration at targeted frequencies stimulate the muscle spindles and create illusions of elbow flexion or extension. These vibrations have been utilized in tasks where subjects must actively move their left limb (for example) to match ongoing movement in the passively moved right limb. As a result, for example, if the right limb is extended 15 degrees in conjunction with specific vibrations, the subject moves their left limb beyond that 15 degrees to match the additional illusory movement (Cody, Schwartz, & Smit, 1990; Cordo, Gurfinkel, Bevan, & Kerr, 1995).

Golgi tendon organs interface between tendons and muscles. They detect load on the limb and are silent when at rest. Their firing frequency increases as muscle tension rises (Proske & Gandevia, 2012; Tuthill & Azim, 2018).

Joint receptors detect when a joint reaches its limit. Their rate of firing reaches its peak at each joints limit. The joint receptors are in fact the same type of sensory neurons associated with tactile sensation: Ruffini endings and Pacinian corpuscles (Tuthill & Azim, 2018). This is an example of “distinct” sensory systems registering overlapping information. In fact, proprioceptors, nociceptors, and touch receptors activate to many similar stimuli.

Proprioceptors are typically discussed in reference to the above three functional groupings, even though each group includes distinct sensory receptors which respond to somewhat difference stimulation. As mentioned before, insect proprioception has been a useful tool in advancing our understanding of human proprioception. Remarkably, insects also have unique sensory receptors that provide similar information to the three functional groups we discussed in humans (muscle stretch, effort, and joint limits). Albeit, insect receptors may acquire information in different ways; for example, while joint limits in humans are detected by receptors in the joints themselves, insects rely on external hair plates which signal joint extremes (Tuthill & Azim, 2018). The nature of the proprioceptive system of the most recent shared common ancestor between humans and insects (a wormlike organisms) is a mystery, though our proprioceptive systems have evolved separately for roughly half a billion years. It is most likely that the striking similarities between human and insect proprioceptors function evolved convergently. Human proprioceptors may not resemble insect sensory organ, and there may be few similarities in how proprioceptive information is processed centrally, though the functional similarities likely reflect an optimal solution to motor control in the face of similar ecological pressures and ethological constraints. The potential value of translating insect research into future studies in humans shouldn’t be dismissed.

Distinguishing peripheral afferents and their contributions to our body estimations is a difficult task. Mechanoreceptors in the skin and interosseous membrane react to vibration and skin deformation; it is possible that they also contribute to the sense of body position and movement. Interestingly, recordings have shown that proprioception and touch may already be integrated within spinal cord and ventral nerve cord (VNC) neurons (Tuthill & Azim, 2018). It is unclear how this integration contributes to proprioceptive control of movement, which raises a number of questions. For example, is “proprioceptive” cortical activation correlated with an integration of assorted somatosensory neurons? To what extent is this integration needed in sensorimotor control? Is there a common coordinate system or frame of reference for proprioceptive information of the limbs? Does it vary from limb to limb? We know that visual signals are in eye-centered coordinates and vestibular signals are in head-centered coordinates (Proske & Gandevia, 2012), so how might proprioceptive signals differ and how might they integrate? These questions are likely to be addressed in animal models and even computational modelling, though they are brought up here to highlight some of the large gaps in knowledge that could certainly hold bearing over rehabilitation research and application.

1.1.5 Measuring proprioception

Clinical measurement of proprioception most often assesses position or movement sense using quick and simple assessments (Sayar & Nübol, 2017). For example, the Finger-Nose task requires the patient to touch the tip of their nose with their index finger after the limb has been passively positioned and while their eyes are closed; another related measure, the Thumb Finding task (also known as the Thumb Localizing Test), requires the patient to locate and pinch their opposite thumb while eyes are closed (Hirayama, Fukutake, & Kawamura, 1999). A range of measures incorporate position discrimination or the detection of movement direction or thresholds, typically at the finger, wrist or elbow while vision of the limb is occluded (Findlater & Dukelow, 2016; Hughes et al., 2015; Lincoln et al., 1991). Unfortunately, these measures have been found to be lacking in numerous ways, including poor sensitivity and interrater reliability (L. M. Carey, Oke, & Matyas, 1996; Connell et al., 2008; Findlater & Dukelow, 2016; Garraway, Akhtar, Gore, Prescott, & Smith, 1976; Lincoln et al., 1991). A concern with these measures is their inability to pick up on subtle differences in proprioceptive capacity; they can identify significant deficits, though may miss impairment that impact limb function.

A number of proprioceptive measures have been developed for research which show greater reliability that are also more informative (L. M. Carey et al., 1996; Leeanne Carey et al., 2011;

LM Carey, Matyas, & Oke, 1993; Collins et al., 2000; Walsh, Proske, Allen, & Gandevia, 2013). While greatly improved over clinical assessments in their capacity to detect subtle differences in proprioception, these measures often examine proprioceptive capacity at isolated joints (finger, wrist, elbow), which may be a limit to ecological validity. We have a poor understanding of how proprioception varies between joints, though it does seem that proprioceptive sensation is calculated differently between joints (Walsh et al., 2013). It remains unknown whether specific joints are better predictors of outcomes than others. Further, proprioception is critically important in motor planning and execution due, in large part, to its role in multi-joint coordination and limb posture (R. L. Sainburg et al., 1995; R. Sainburg, Poizner, & Ghez, 1993). Measures requiring full limb movement using robotic assessment help remedy this concern, though even then the apparatus confine movement to a horizontal plane within a limited range of movement (Cusmano et al., 2014; Dukelow et al., 2010; Scott & Dukelow, 2011; Semrau, Herter, Scott, & Dukelow, 2013, 2017). These research measures, while more reliable and informative than clinical assessments, are often not employed in rehabilitation settings due to time costs, and in the case of robot assessments, actual cost and portability (Findlater & Dukelow, 2016).

Our clinical practice will benefit from further basic research, though as it stands, we can also apply existing evidence to developing improved patient-centered measures. For example, it seems plausible that measures of multi-joint position/posture may better reflect upper-limb function than single joint measures. Another example, evidence suggests that we have better access to effector endpoint position than joint angles (Fuentes & Bastian, 2009). In their experiment, arm configurations were adjusted passively at the elbow using a robotic exoskeleton and the subjects were asked to estimate the position of their fingertip or the angle of their elbow (all other factors remained consistent). Should we be looking at perception of endpoint position or movement instead? Yet, many measures of proprioception used in research rely on joint angle estimates. It is unclear whether stroke survivors with proprioceptive deficits show a similar disparity between endpoint and elbow estimation and whether assessments of proprioceptive capacity/deficit focusing on endpoint would better reflect outcomes of interest.

Clinical research suggests proprioception can have a serious impact on outcomes such as upper limb quality of movement and engagement in activities of daily living (Meyer, Karttunen, Thijs, Feys, & Verheyden, 2014), though, it is difficult to draw specific conclusions with a single brief clinical test or the many varied forms of joint angle matching or movement detection. The concern being: multi-factorial studies of stroke-deficits and their impact on clinically relevant outcomes might obfuscate the importance of proprioception when “study A” includes a measure of elbow joint angle perception and “study B” uses a measure of index finger movement detection. Both measures assess a proprioceptive modality, though one may assess a modality with far greater bearing on functional outcomes, or perhaps each modality impacts disparate outcomes or the same outcome in unique ways. These examples are likely understating the problem: proprioceptive modalities overlap and diverge in complex ways (Proske & Gandevia, 2012, 2018; J. L. Smith et al., 2009; Walsh et al., 2013).

Improving measures so that they can detect subtle changes in deficit or better reflect the proprioceptive skills important in our clinical outcomes of interest is not the only concerning matter. Beckoning back to Section 1.1.3 on the concerns of psychophysics, there is the issue of perception versus sensation, which raises the question: “how useful are our measures of proprioception, which typically rely on an individuals’ perceived position, posture, or movement?” Though finding ways to assess proprioceptive sensation, without relying on perception is not a trivial matter (and may be impossible in many cases). There are clever studies which have scratched the surface of the unconscious role of proprioception in the planning and control of movement. In a study by Patterson et. al. (Patterson et al., 2017) repeated out and back reaching movements from a start point to a target point in the absence of visual feedback resulted in reliable limb drift. Despite this drift, the angle of reaching trajectory remained consistently accurate. An accurate trajectory would require accurate joint angle information to plan the multi-joint torques needed. So, accurate proprioceptive information was available to plan movement trajectory but couldn't be accessed to prevent position drift. With those sorts of inconsistency in unconscious motor planning, what disparities might there be between sensation and perception?

I argue that research needs to follow two lines of inquiry, 1) identifying and distinguishing the mechanisms of proprioception in the planning and control of action, and 2) working to develop measures which reflect the features of proprioception linked to our behaviors of interest (upper-limb performance). For example, visual or motion-based AI has advanced dramatically in recent years and may be used to record detailed body kinematics over extended periods of time in patients' natural environments (Chen P-W^{CO}, Baune NA^{CO}, Zwir I, Wong AWK, Manuscript in Progress). It would be wise to apply these advances to the many ethologically relevant behaviors regulated by proprioception—as soon as we find out what those behaviors are.

1.2 Motor planning and control: flexible yet distinct roles of proprioception and vision

Planning your reach and/or grasp requires information about the target as well as an estimate of your current bodily configuration (e.g., where is my arm, are my fingers ready to grasp, and will I need to lean forward?). Most often you assimilate visual information to determine relevant features of the object, though you can also rely on memory if needed. You have an ongoing estimate of the position and orientation of your body parts based on an integration of information from peripheral afferents, the visual and vestibular system, and your past or ongoing motor commands. Efferent signals from your brain trigger the muscles in your arm to act, all according to a motor plan. You are halfway there, but you run into unexpected circumstances: the napkin you were reaching for is caught by the wind and, if that wasn't enough, you are fatigued from yesterday's workout (the first in years). Luckily, these sorts of unexpected occurrences are dealt with without any thought on your part. You may not always succeed, though you are able to cope surprisingly well. How is that?

1.2.1 Feedback and feedforward control

In the case that something unexpected arises, depending on how much time you have to correct, sensory feedback may allow you to recognize the discrepancy between your goal and your motion, and update your plan accordingly: this is feedback control.

Sensory afferents take time to reach the brain, and this isn't the only form of delay between the stimulation of peripheral receptors and an appropriate motor response. Once afferent signals are received, there is a period before efferent signals reach and activate the muscles in the arm. And so, there are instances where we are locked into our current motor plans. It is estimated that upper-limb control contends with <=100ms delays in sensory feedback (Frédéric Crevecoeur, Munoz, & Scott, 2016). A delayed response of 100ms could be the difference between successful or unsuccessful action/reaction. To compensate, the brain estimates sensory time delays, as well as ongoing and expected future sensory states, in order to perform optimal control (Frédéric Crevecoeur et al., 2016; Sargolzaei, Abdelghani, Yen, & Sargolzaei, 2016).

As with all estimates, they can be more or less accurate. For example, while trying to thread a needle, the most minute movement of the limb causes you to overshoot and the tip of the thread flies past the needles eye. This is a difficult task, and while a tailor may be able to thread the needle in one motion, you watch as you repeatedly fail. In this example, visual feedback is informing us that we have made an error and need to correct. As we move the thread closer, we adjust, and even then, we fail because the motor correction/adjustments weren’t optimal. In summary, feedback is used to correct ongoing actions, as well as adjust how we will respond to future feedback (i.e., sensorimotor learning).

Yet feedback control isn’t always an option. We have seen this in the case-study of an allograft (donor) hand transplant recipient. The subject had to compensate for reinnervation errors in the hand and possibly persistent maladaptive neuroplastic changes in primary somatosensory cortex (S1). As a result, the patient’s reach to grasp movements were rapid and their grasp aperture was significantly larger than healthy controls, both signs of a reliance on feedforward/ballistic movement strategies in the face of unreliable somatosensory feedback (Valyear, Mattos, Philip, Kaufman, & Frey, 2017). When sensory deficits aren’t a factor, our brain continuously vets the expected sensory outcomes against actual outcomes, meaning we aren’t relying on feed-forward control for long.

It is difficult to formulate what will result in successful motion when we must consider environmental factors as well as possible sensory deficits. When do we rely on vision? When do we rely on ballistic/feed-forward control? How does proprioception fit in?

1.2.2 Vision versus proprioception

There is evidence that upper-limb actions predominately rely on proprioceptive afferents for feedback control in healthy adults, at least in simple reaching tasks (Frédéric Crevecoeur et al., 2016). Yet, another study reported no change in reaching when proprioception is disturbed using vibration of muscle spindles, concluding that vision is the primary source of feedback used in error detection during simple reaching tasks (Goodman et al., 2018). So, which is it?

We often reach and grasp objects in the absence of vision of the hand, and research indicates that the removal of such visual feedback has only modest effects on timing and precision in healthy adults (Goodale, Pélisson, & Prablanc, 1986; Reichenbach, Thielscher, Peer, Bülthoff, & Bresciani, 2009). In fact, studies of hand-eye coordination have found that even during visually guided grasp, we do not fixate on the hand, but instead our gaze leads the hand, fixating on landmarks that are critical to the action goal (Hesse & Deubel, 2009; Johansson, Westling, Bäckström, & Flanagan, 2001). Hall et al. (Hall, Karl, Thomas, & Whishaw, 2014) found that humans can successfully reach to grasp objects in the periphery (where only peripheral visual feedback is available) and that visual fixation of object landmarks appears to be involved in functions of grasp formation, as denial of visual fixation of the object results in haptic exploration following successful transportation. Such evidence could lead to the conclusion that vision of the limb doesn’t factor into reaching. An alternative interpretation, supported by complementary research (Fleishman & Rich, 1963; Law, Atkins, Kirkpatrick, & Lomax, 2004), is that healthy individuals who haven’t lived with persistent proprioceptive deficits can rely on either source of sensory feedback to guide their movements during familiar tasks.

A study in healthy adults found a significant effect of baseline proprioceptive and visuo-spatial capacities on performance and learning of a challenging bimanual task. In brief, visuo-spatial capacity was associated with superior performance in early trials, whereas proprioceptive capacity was associated with superior performance in later trials, after repeated exposure and training on the task (Fleishman & Rich, 1963). It is possible that vision of the limb is relied on to accomplish untrained tasks, whereas proprioceptive feedback is the preferred source of feedback when performing a highly trained task. The cited study relied on a novel and difficult task, though this isn't usually the case in reach and grasp research. The tasks used in most studies of reaching and grasping are underwhelmingly simple; healthy adults (or healthy research macaques that reach and grasp full-time) could be considered experts in remaining seated while reaching and grasping a small object that appears in predictable locations—trial after trial. As another example, a study found correlations between visual monitoring behavior and expertise in surgeons, with novice surgeons occasionally monitoring their hands and tools (as well as making more errors) while expert surgeons rarely focused on their bodies or tools, presumably relying on non-visual mechanisms such as proprioception and feedforward control (Law et al., 2004). Essentially, during simple or highly trained tasks, we rarely visually monitor our bodies, though this is not the case for untrained tasks.

While there may be situations where vision can fill the role of proprioceptive feedback, this isn't always the case. In our case report of the hand transplant patient, they had full vision of the hand during reach and grasp, yet their kinematics suggested they were relying on ballistic/feedforward control for reaching (Valyear et al., 2017). Proprioceptive feedback is an important component in motor learning. It is needed to build efficient motor commands, though it also appears to be critical in execution. Patients with sensory neuropathy who show targeted loss of somatosensory afferents without impairment to motor systems rely on visual feedback regardless of how simple or skilled they were in the task prior to injury. Without proprioception, their movements are clumsy (Ghez, Gordon, & Ghilardi, 1995b; Gordon, Ghilardi, & Ghez, 1995b; Messier, Adamovich, Berkinblit, Tunik, & Poizner, 2003; J. Rothwell et al., 1982; Sarlegna, Gauthier, Bourdin, Vercher, & Blouin, 2006). This suggests that proprioceptive feedback is uniquely important in the execution of skillful motor commands; visual feedback alone isn’t enough.

Reliance on visual feedback for movement is taxing and inefficient (Scott, 2016) and visual feedback is delayed relative to proprioception, albeit the difference seems to be ~10ms (Frédéric Crevecoeur et al., 2016). It is tempting to postulate that becoming skilled in a task reflects a transition from inefficient to efficient strategies of control, where visual feedback is optimal during early learning and proprioception is necessary for skilled performance, though currently we can only speculate. Vision appears to be critical in planning movement trajectories in coordination with body estimates of starting limb configuration built from proprioceptive information and proprioception is used for online correction during rapid movements (Bagesteiro, Sarlegna, & Sainburg, 2006; Sarlegna & Sainburg, 2009). Proprioception is important in translating visual information relevant to our goal into a motor plan.

Vision has been shown to be sufficient in updating motor plans in healthy individuals, though for some reason persistent proprioception deficits lead to difficulties that vision can’t overcome (Ghez et al., 1995b; Gordon et al., 1995b; R. L. Sainburg et al., 1995; Semrau, Herter, Scott, & Dukelow, 2018). While further research is necessary, there are a few plausible hypotheses that can be formed based on the existing research: 1) visual and proprioceptive feedback are critical to building effective motor commands in adults without visual or proprioceptive deficits, and 2) reliance on visual or proprioceptive feedback depends on the actors’ skill, where visual feedback is important in untrained tasks and proprioceptive feedback is necessary for task mastery; this may be a mechanism underlying the transition from unskilled to skilled performance.

Further studies in healthy adults would benefit from more difficult tasks, possibly requiring object interaction or tool use. Perhaps then the distinguishing features of visual and proprioceptive feedback in motor planning and control would be more obvious. Though existing studies in patients with proprioceptive deficits, even those relying on simple tasks, allow us to observe changes in performance under varied reaching and grasping conditions.

1.3 Proprioception and stroke rehabilitation

1.3.1 Prevalence

An estimated 50% of stroke survivors show signs of proprioceptive deficits following injury (Leeanne Carey et al., 2011; LM Carey et al., 1993; Dukelow et al., 2010; Findlater & Dukelow, 2016; Hughes et al., 2015; Semrau et al., 2013). Estimates vary due to methodology inconsistencies and actual prevalence could be higher (Connell et al., 2008); in a study of 70 stroke survivors, Connell et al. (2008) reported that all showed some degree of impairment in various proprioceptive and somatosensory measures compared to healthy adults (who performed maximally).

1.3.2 Impact of proprioceptive deficit in stroke

Rehabilitation research into proprioception predominately focuses on the lower-limb and balance, which isn’t a fault given that the natural decline in proprioceptive capacity as we age is linked with the prevalence of falls (Proske & Gandevia, 2012). Though proprioception is incredibly important in upper-limb control as well, including learning and mastery of skilled actions in healthy adults and stroke survivors (Fleishman & Rich, 1963; Vidoni & Boyd, 2009).

Proprioceptive impairment can have serious impacts on upper limb function (Feys, Hees, Bruyninckx, Mercelis, & Weerdt, 2000; Paci et al., 2007; Rand, Weiss, & Gottlieb, 1999), quality of movement (Park et al., 2008), and performance in activities of daily living (Desrosiers, Noreau, Rochette, Bravo, & Boutin, 2002; Morris, Wijck, Joice, & Donaghy, 2012). A meta-analysis of studies on somatosensory deficits, including the previously cited studies, and their impact on varied outcomes found a significant correlation between proprioception and upper-limb usage and quality of movement (Meyer et al., 2014). Further, proprioceptive deficit has been linked to the length of hospital stay (Chester & McLaren, 1989) and extended recovery times (Semrau, Herter, Scott, & Dukelow, 2015).

Given the importance of proprioception in motor learning and capacity for upper-limb performance (Fleishman & Rich, 1963; Vidoni & Boyd, 2009), proprioceptive deficits are likely a significant contributor to stroke survivors difficulties in recovering a satisfactory degree of upper-limb performance in coordinated tasks (Broeks, Lankhorst, Rumping, & Prevo, 1999; Fullerton, Mackenzie, & Stout, 1988; Morris, Wijck, Joice, & Donaghy, 2013; Prescott, Garraway, & Akhtar, 1982; Tyson, Hanley, Chillala, Selley, & Tallis, 2007; Wade, Langton-Hewer, Wood, Skilbeck, & Ismail, 1983; Weerdt, Lincoln, & Harrison, 1987).

Further research is needed to link proprioceptive modalities with clinically relevant outcomes. Though these correlations alone aren’t enough. If we want to apply our research to advancing sensorimotor rehabilitation practice, we will need a better understanding of how proprioceptive deficits impact strategies of motor control.

1.3.3 Altered motor control strategies

As mentioned in section 1.2.2, large-fiber neuropathy patients with a total loss of somatosensory afferents rely on visual feedback to monitor their limbs mid-action. Visual monitoring is an inefficient and taxing strategy (F Crevecoeur & Scott, 2013; Frédéric Crevecoeur & Scott, 2014; Gentilucci, Daprati, Gangitano, Saetti, & Toni, 1996) and the delays in visual feedback relative to proprioception are of a magnitude which could impact rapid movement correction (Scott, 2016). While, in these individuals, visual monitoring results in immediately improved performance, it does not allow for optimal patterns of movement (R. L. Sainburg et al., 1995; R. Sainburg et al., 1993). These shortcomings could lead to potentially harmful outcomes such as interfering with our ability to monitor our surroundings and even serious injury.

There is a dearth of research that ties the compensatory strategies which follow proprioceptive impairment with real-world outcomes. Further, we aren’t sure how the degree of proprioceptive deficit, such as minor decline in aging or varied impairment in stroke survivors, impacts both motor control strategies and real-world outcomes. However, there is recent evidence of visual compensatory strategies in stroke survivors with proprioceptive deficits and a reliance on visual feedback during upper-limb control of action using planar robots (Semrau et al., 2018). Unfortunately, these very studies conclude that visual feedback is not enough to compensate for proprioceptive loss, in which case we must look towards possible targeted treatments to see whether proprioceptive function can be improved.

1.3.4 Prospect for recovery or improvement

Proprioceptive deficits have typically not been utilized as prognostic indicators of stroke outcomes (Findlater & Dukelow, 2016), despite their strong link with clinically meaningful outcomes. The nuanced and diverse ways in which common stroke comorbidities may manifest suggests that any one deficit is likely to be a poor prognostic indicator.

This may be in part due to the low-sensitivity measures often used in stroke outcome measurement, such as the Modified Rankin (Quinn, Dawson, Walters, & Lees, 2009; Saver et al., 2010; Wilson et al., 2005), which is a measure of disability and dependence in daily activity and has become the most widely used measure in stroke clinical trials. The Modified Rankin provides a holistic assessment of a patient's functional independence, which is undeniably important, though simplistic outcome measures are likely to miss significant gains from targeted therapies. In stroke especially, attention to the many potential deficits is needed during rehabilitation, especially since many impairments can impact similar outcomes, for example, performance on more complex motor tasks could be impacted by sensorimotor deficits as well as impaired cognition. Significant improvements in upper limb function from a intervention that targets proprioception may not be enough to warrant a shift on the Modified Rankin's 7-point scale, where a rating of 0 reflects "No symptoms at all" and 6 means you are "Dead".

Despite the difficulties of discerning significant gains in stroke, there is evidence that improvements in proprioceptive capacity are possible (L. M. Carey & Matyas, 2005; Leeanne Carey et al., 2011; LM Carey et al., 1993; Smania, Montagnana, Faccioli, Fiaschi, & Aglioti, 2003; Yekutiel & Guttman, 1993; Yozbatiran, Donmez, Kayak, & Bozan, 2006). Currently, the common approach to dealing with proprioceptive deficits in therapy is to teach patients to compensate using visual feedback (Abdollahi et al., 2013), a strategy which we have stressed in sections 1.2.1and 1.2.2may not be ideal in long term recovery.

1.3.5 Proprioceptive deficit and neural injury

Proprioceptive deficits may arise following many forms of neurological injury, including spinal cord injury, large fiber neuropathy, Parkinson’s Disease, traumatic brain injury, and stroke. Proprioceptive processing is widespread, damage to the parietal cortex, primary sensorimotor cortices, thalamus, medulla, and other regions of the nervous system can result in proprioceptive deficits (Proske & Gandevia, 2012, 2018; Tuthill & Azim, 2018). For example, damage to the spinal cord may disrupt or alter afferent proprioceptive information en route to the central nervous system (Gordon et al., 1995a; J. Rothwell et al., 1982; R. Sainburg & Ghilardi, 1995; R. L. Sainburg et al., 1995). Damage at the level of the thalamus or medulla caused by a stroke can similarly lead to proprioceptive deficits, and such lesions often express themselves with fairly isolated sensory deficits, though such cases are exceedingly rare (J. Kim, Kim, & Chung, 1995; Sacco, Bello, Traub, & Brust, 1987).

The most common cause of proprioceptive deficits in stroke is thought to be attributed to damage in the posterior parietal cortex (Findlater et al., 2016; Kenzie, Findlater, Pittman, Goodyear, & Dukelow, 2019; Pause, Kunesch, Binkofski, & Freund, 1989). While it is unclear what proportion of stroke survivors with parietal strokes experience proprioceptive deficits, it is clear that damage to the parietal cortex can also lead to a number of other impairments such as visual-spatial neglect, impaired executive-function, emotional dysregulation, bodily weakness, and depression. This makes it very difficult to isolate proprioceptive deficits in our research.

While there isn’t a clear neural center for proprioceptive processing, uncovering its neural underpinnings can still inform us in a number of ways, including our understanding of multi-sensory integration and allow us to better predict sensorimotor performance following stroke.

1.4 Control of reach/grasp: neural correlates

Researchers have identified parieto-frontal networks involved in reaching and grasping in human and non-human primates; these networks share many similarities, and often human research attempts to replicate findings from previous non-human primate research. These networks include substantial regions of the posterior parietal and premotor cortices, with evidence for distinct functional roles within, as well as implications in other regions. (Begliomini, Caria, Grodd, & Castiello, 2007; Begliomini et al., 2014; Begliomini, Wall, Smith, & Castiello, 2007; Binkofski, Buccino, Posse, et al., 1999; Binkofski, Buccino, Stephan, et al., 1999; Binkofski, Dohle, Posse, Stephan, & Hefter, 1998; Castiello & Begliomini, 2008; Culham, Cavina-Pratesi, & Singhal, 2006; Culham & Valyear, 2006; Gallivan, McLean, & Culham, 2011; Gallivan, McLean, Valyear, Pettypiece, & Culham, 2011; S. Grafton, Arbib, Fadiga, & Rizzolatti, 1996; S. T. Grafton, Fagg, Woods, & Arbib, 1996; James, Culham, Humphrey, Milner, & Goodale, 2003; M Jeannerod, Arbib, Rizzolatti, & Sakata, 1995; Monaco et al., 2011; Monaco, Sedda, Cavina-Pratesi, & Culham, 2015; Rossit, McAdam, Mclean, Goodale, & Culham, 2013; Eugene Tunik, Frey, & Grafton, 2005; Eugene Tunik, Ortigue, Adamovich, & Grafton, 2008; Valyear, n.d.).

While human and non-human studies have traditionally examined visually guided reach/grasp behaviors, there is evidence suggesting that neurons in monkey anterior intraparietal area (AIP) are not solely concerned with extrinsic (visual) features relevant to grasping (Murata, Gallese, Kaseda, & Sakata, 1996; Sakata & Taira, 1994); intrinsic information (e.g., proprioceptive) regarding the upper limb also contribute, though the same has not been confirmed in humans.

In chapter 2 of this dissertation, I hypothesize that subregions of the frontoparietal circuit, including subsets of the anterior intraparietal sulcus (aIPS; similar to monkey AIP) and superior parietal occipital cortex (SPOC) participate in the control of grasping even when visual feedback is eliminated. This would suggest that these regions' functions are not concerned solely with vision and utilize other sources of information to represent grasp accurately. Identifying the neural regions involved in non-visually guided grasping, beyond filling in a gap in our basic understanding, could better our understanding of the outcomes expected following neural insult, and maybe one day guide neurorehabilitation.

1.4.1 Reach and grasp in nonhuman primates: parieto-premotor circuits for sensory-to-motor transformations

Early studies identified neurons in monkey intraparietal sulcus (AIP, LIP, CIP) and superior parietal lobule (SPL) with the visual guidance of reaching; they found that the neurons within were not simply sensory in nature but were involved in sensorimotor integration (Hyvärinen & Poranen, 1974). Not long after, Mountcastle et al. reported "hand manipulation" neurons within the same regions. These neurons responded immediately prior to and during manipulation of an object (Mountcastle, Lynch, Georgopoulo, Sakata, & Acuna, 1975).

Later evidence found activity of neurons within the monkey AIP which correlated with grasp specifically, yet not reach. Research by Sakata and colleagues was among the first to identify monkey area AIP as important in goal-directed grasping (Gallese, Murata, Kaseda, Niki, &

Sakata, 1994; M Jeannerod et al., 1995; Murata et al., 1996; Murata, Gallese, Luppino, Kaseda, & Sakata, 2000; Sakata & Taira, 1994; Sakata, Taira, Kusunoki, Murata, & Tanaka, 1997; Sakata, Taira, Murata, & Mine, 1995; Taira, Mine, Georgopoulos, Murata, & Sakata, 1990). They looked at visual and motor responses of neurons separately within AIP by training macaques to either gaze or grasp objects in the light or in the dark (with a very dim LED on the surface of the object to help with location). In these studies, great care was taken to ensure that the object was not visible during the dark phases. They found that many neurons were responsive to particular grasp configurations in relation to the object shape. Further, neurons' receptive field properties were found to belong to one of three types, "visual", "motor", or "visual/motor". Visual neurons responded only to vision of a given object, though not to manipulation. Motor neurons responded only during the grasp of an object. Visual/motor neurons responded both to vision and grasp of the same object. Further, the neurons Sakata labeled as "motor-dominant," were fully active during grasp in the dark and the level of activity was the same as when grasping in the light, which suggests that neurons in this region may be performing sensorimotor transformations on non-visual representations. The causal relationship between these responses and behavior was subsequently established by demonstrating grasp-specific functional deficits following injections of muscimol (an agonist of the inhibitory neurotransmitter GABA) to selectively disrupt AIP in monkeys trained to grasp objects, resulting in impaired grasping, without a deficit to the monkeys reaching ability (Gallese et al., 1994).

Monkey AIP shares dense reciprocal connections specifically with area F5 in the ventral premotor cortex (Borra et al., 2008; Luppino, Murata, Govoni, & Matelli, 1999; Matelli & Luppino, 2001). Neurons within F5 show very similar response characteristics to those in AIP; F5 also contains neurons that respond selectivity for particular objects, with close matching of visual and motor response specificity (Murata et al., 1997; Raos, Umiltá, Murata, Fogassi, & Gallese, 2006; Rizzolatti et al., 1988, 1996) and similar to AIP, inactivation of F5 through muscimol injections has been found to disrupt hand pre-shaping during grasping (L Fogassi et al., 2001).

It has been suggested that multisensory information regarding external objects are processed in the posterior parietal cortex (PPC), which heavily influences F5 and that F5 is involved in action selection, which is relayed to primary motor area M1 (Dancause et al., 2006; M Jeannerod et al., 1995; Spinks, Kraskov, Brochier, Umilta, & Lemon, 2008; Umilta, Brochier, Spinks, & Lemon, 2007). Though, if the PPC is processing more than just extrinsic sensory information, we would also expect activity in F5 correlated with intrinsic information. In fact, Macaque F5 has been implicated in coordinating visual and proprioceptive information to determine arm location, though whether it shows activity correlated with proprioception in grasp is unknown (Graziano, 1999).

AIP and area F5 have a substantial amount of evidence implicating their involvement in prehension, though other cortical (and subcortical) regions are no doubt involved. For example, evidence indicates that area F2, or the dorsal premotor cortex, is also important for the control of grasping (S. T. Grafton, 2010; Matelli & Luppino, 2001; Raos, Umiltá, Gallese, & Fogassi, 2004) and evidence from electrophysiological studies indicate that medial posterior parietal area V6A, previously thought of as being selectively involved in reaching and arm control, shows response coding for monitoring and correcting for errors in the spatiotemporal features of the hand during reaching and grasping (Breveglieri, Bosco, Galletti, Passarelli, & Fattori, 2016; P Fattori et al., 2010; Patrizia Fattori, Breveglieri, Amoroso, & Galletti, 2004; Galletti, Kutz, Gamberini, Breveglieri, & Fattori, 2003). Activity related to grasping has also been observed in the inferior parietal lobule (IPL), with neurons displaying different response profiles based on the action goal (e.g., grasping to eat versus grasping to place), as well as firing during the observation of actions performed by others (Leonardo Fogassi et al., 2005).

There are limitations to electrophysiology studies in monkeys or single-unit recordings in general. While you gain incredible spatial and temporal resolution with the method, it is very focal, meaning other cortical regions could be involved, though would not be noticed unless specifically tested. Further, while there are many parallels between the monkey reach and grasp network and the human network, caution should always be taken when generalizing findings to humans. There are many differences between human and non-human primate physiology. Testing hypotheses concerning humans that were formed based on the non-human primate is a necessary step.

1.4.2 Grasping in humans

Despite an estimated gap of 30 million years since we last shared a common ancestor with macaques, evidence suggests that the anterior intraparietal sulcus (aIPS) and ventral premotor cortex (vPMC) in humans may be functionally similar to monkey AIP and F5, respectively (Cisek & Kalaska, 2010; S. T. Grafton, 2010; Johnson-Frey et al., 2003).

Much of the research on human grasp has built off the original and ongoing research in non-human primates and most of this human research has involved functional neuroimaging. A benefit of neuroimaging over single-unit recording methods includes the ability to capture data from the entire brain non-invasively (and thus in humans), though at the cost of relatively worse temporal and spatial resolution.

Initial efforts to localize a homologue of monkey AIP within human anterior intraparietal sulcus (aIPS) involved positron emission tomography (PET) imaging of cerebral blood flow during tasks that required grasping objects compared to pointing at objects. Grasping typically resulted in a relative increase in blood flow in a broad region that encompassed the postcentral sulcus. Activity in IPS and the inferior parietal lobule (IPL) was also correlated with imagined grasp (Decety, 1996). As well, vPMC and inferior frontal gyrus (IFG) activity was correlated with observation of grasp (S. Grafton et al., 1996). Numerous fMRI studies have since identified human aIPS in grasping compared to simply reaching to touch or point at an object (Begliomini, Caria, et al., 2007; Begliomini, Wall, et al., 2007; Binkofski, Buccino, Posse, et al., 1999; Binkofski, Buccino, Stephan, et al., 1999; Binkofski et al., 1998; Frey, Vinton, Norlund, & Grafton, 2005)

A limitation of functional neuroimaging is its correlational nature. Evidence for the causal role of PPC comes from studies of grasp in patients with focal brain injuries. Jeannerod et al. reported a case study in which a patient with a bilateral PPC lesion exhibited a marked deficit in the ability to grasp simple objects, while their ability to reach for the same objects was unimpaired (M Jeannerod, Decety, & Michel, 1994). Evidence also suggests that the PPC is important in proprioception, as seen in patients suffering from optic ataxia. Optic ataxia is a disorder brought about by damage to the dorsal PPC. Patients with optic ataxia suffer from manual mis-reaching errors to visual targets, even though their primary sensory and motor functions remain intact. A study by Blangero et al. found that a group of optic ataxic patients also performed poorly on a proprioceptive task where they were required to touch the tip of one index finger to the other without use of vision (Blangero et al., 2007), with the authors suggesting that optic ataxia may not be a purely optic issue.

Causality between aIPS and grasp can also be tested in healthy individuals using transcranial magnetic stimulation (TMS). TMS can be used to disrupt aIPS during prehension. A study by Tunik et al. had subject's reach and grasp a bar, which on some trials rotated, requiring online correction. TMS was applied at various delays after object perturbation. If the TMS pulse was within 30ms after object perturbation subjects showed a deficit in grasping, without impairment to reaching, though if the TMS pulse came at later delays (65ms, 80ms, or 95ms) the deficit was not observed (Eugene Tunik et al., 2005). This suggests that aIPS may be involved in error-detection processes related to grasp. The authors later comment that aIPS appears to be "performing dynamic, goal-based, sensorimotor transformations that involve at least three variables: the current sensory state of the actors body (context), the current motor command and the current goal" (E Tunik, Rice, Hamilton, & Grafton, 2007).

There is evidence that suggests aIPS is coding for more than just the visual sensory modality, but it is also involved in the association or combination of the multiple modalities in a way that is important to grasp. Grefkes et al. presented objects to subjects briefly, took the object away, and replaced it with either the same or a different object. The subject's task was to identify whether the second presented object was the same as the first. Notably, subjects had to inspect the objects either visually or haptically (without vision). Grefkes found that aIPS was active both when identifying the first and second object purely visually or purely haptically, though greater activation was found when modalities were crossed so that an object initially assessed visually or haptically had to be identified with the opposite modality on the follow up presentation (Grefkes, Weiss, Zilles, & Fink, 2002).

A study by Frey et al. (Frey, Hansen, & Marchal, 2015) recorded activity with fMRI during tasks in which healthy adults performed goal-directed reach and grasp actions manually or by depressing buttons to initiate the same behaviors in a remotely located robotic arm (arbitrary causal relationship). Frey detected greater activity in aIPS during manual grasp versus reach (when proprioception was involved), however, in contrast to prior studies involving tools controlled by nonarbitrarily related hand movements (also involving proprioception)(Gallivan, McLean, Valyear, & Culham, 2013; Jacobs, Danielmeier, & Frey, 2010), responses within aIPS and premotor cortex showed no evidence for selectivity for grasp when participant's employed the robot (when there is visual, but no proprioceptive, feedback relevant to grasping).

Interestingly, neuroimaging studies in humans have consistently identified aIPS in a reach-to-grasp task; yet significant activation of vPMC has been reported much less consistently (Begliomini, Caria, et al., 2007; Begliomini, Wall, et al., 2007; Frey et al., 2005; S. T. Grafton et al., 1996). There are several possible reasons for this, which Begliomini details, including the possibility that due to the tendency to subtract reach activation from grasp in fMRI analysis the vPMC activity, which tends to be present for both reach and grasp, is cancelled out (Castiello & Begliomini, 2008). While grasp tasks in human fMRI have not consistently linked vPMC, it may still be involved in similar ways to those identified in monkey area F5. Binkofski et al. found activation of vPMC when manipulating complex objects, without vision, compared to a simple sphere or rest (Binkofski, Buccino, Posse, et al., 1999). This suggests that vPMC is involved in non-visual sensory transformations. Human fMRI adaptation studies have also shown that vPMC adapts with repeated exposure to a certain grasp axis, but not to a particular object, suggesting that vPMC is more closely related to the motor solutions for prehension of an object and not the specific object itself.

The targets of goal-directed action can be encoded in either allocentric coordinates (relative to a visual landmark) or egocentric coordinates (relative to the actor). It is necessary for allocentric coordinates to be converted into egocentric coordinates for action planning and execution. One study associated left superior parieto-occipital cortex (SPOC), similar to monkey V6A, with coding targets for grasping in an allocentric reference frame, left anterior precuneus and premotor areas with coding targets in an egocentric reference frame, and aIPS as playing a possible transitory role between the allocentric and egocentric specific motor areas (Leoné, Monaco, Henriques, Toni, & Medendorp, 2015).

Further evidence from human neuroimaging studies has suggested that regions previously believed to be involved in visually guided reach and grasp are activated under other sensory circumstances. Monaco et al. (Monaco, Gallivan, Figley, Singhal, & Culham, 2017) identified several novel findings related to tactile and visual exploration of objects: the occipital pole showed greater activation for tactile than visual exploration, though the object was unseen and located in the peripheral visual field; the occipital tactile-visual area (LOtv) exhibited similar activation for both tactile and visual exploration; the Occipital Pole showed greater functional connectivity with aIPS and LOtv during haptic exploration than visual exploration of the shapes in the dark.

While this dissertation specifically focuses on reaching and grasping, there have been a number of studies looking at passive movement of the elbow (Radovanovic et al., 2002; Weiller et al., 1996), wrist (Alary et al., 1998; Ward et al., 2006), and finger (Chang et al., 2009) that have identify activity in many of the same fronto-parietal reach/grasp regions, including S1, M1, and the inferior parietal lobule (IPL). Additional regions have been implicated in passive movements, including the supplementary motor area (SMA) and the premotor cortices (PMD and PMV)(Alary et al., 1998; Radovanovic et al., 2002). Another study used a different task during fMRI. They passively moved the participants wrist while the participant mirrored the movement with the opposite wrist. In healthy controls they found activity in the supramarginal gyrus (SMG) of the IPL and dPMC, and in stroke patients with proprioceptive deficits they reported similar results as well as reduced bilateral activation of SMG, possibly caused by reduced sensation (Ben-Shabat, Matyas, Pell, Brodtmann, & Carey, 2015)

1.5 Conclusions

Understanding proprioception on a neural basis is difficult for a reason. We haven't demonstrated central networks or circuits in the brain dedicated to bodily movement or position based predominately on proprioception, and they may not exist given the intermediary role proprioception is thought to play in integrating multiple sensory modalities for motor control. Signals correlated with proprioceptive processing in the primate cerebral cortex and even insect central complex don't follow a clear topographical representation, making it difficult to analyze the neural bases of proprioception on a population level (Tuthill & Azim, 2018). Neural regions tied to proprioception through functional neuroimaging are typically regions known to be involved in multi-sensory integration and/or complex processes related to action planning and control, which make it difficult to draw conclusions unique to proprioceptive sensation; research in non-human primates may have an advantage in teasing apart nuanced functional correlates in the cortex. While there are numerous regions in the parieto-frontal network that might be involved in non-visually guided reach or grasp, including results from reaching and grasping tasks, as well as passive joint movement, there are still questions that need answered. Results from grasping tasks, for example, remove vision of both the object and the limb, thus, activation could be related to memory-guided grasping.

In conclusion, proprioception is critically important in motor planning, control, and learning. Many patient groups live with proprioceptive impairments. While evidence is building that links proprioception to clinically relevant outcomes, specific conclusions are difficult to draw given the wide range and limitations of existing proprioceptive measurements. Based on existing evidence, there may be targeted ways to improve proprioceptive measurement. Further, there is scant evidence linking subtle changes in proprioceptive deficits with upper-limb performance. It is unclear whether lesser deficits, such as seen in proprioceptive decline as we age (Adamo et al., 2007; Ribeiro & Oliveira, 2007; Shaffer & Harrison, 2007), negatively impact individuals; stroke patients also show varying degrees of deficit. It is unclear how these varied impairments affect motor control strategies, such as relying on visual feedback or ballistic movements. Studying the type of actions which these deficits affect most and how patients are compensating to overcome their disability could have a direct impact on rehabilitation practices. Lastly, we have a long way to go in understanding the neural basis of non-visually guided control of functionally relevant actions, such as grasping novel shapes or interacting with objects. The neural correlates may reveal additional information that is of behavioral or clinical relevance, not to mention, as neurorehabilitation continues to advance, having a better understanding of these networks and their specializations may aid in advanced treatment or patient care.

Chapter 2: Full Upper-Limb Posture Matching (FULPM): a novel measure of upper-limb position sense.

Proprioception—our sensations and perceptions of bodily position, movement, and effort—is a critical component in the acquisition and maintenance of upper-limb motor skills. Proprioception is complex; it represents a multitude of arguably distinct sensations and perceptions, with position sense and movement sense being the most commonly studied; relative to movement and position sense our sense of effort, force, and heaviness are seldom addressed in the proprioception literature (Bertrand et al., 2004; S C Gandevia & McCloskey, 1977; Lin et al., 2015). Our bodily senses play an important role in motor planning (R. Sainburg et al., 1993), execution (Frédéric Crevecoeur et al., 2016), and learning (Fleishman & Rich, 1963; Vidoni & Boyd, 2009); and so it may not be a surprise that proprioceptive deficits, such as are commonly seen in stroke survivors, can have major impacts on upper limb function (Feys et al., 2000; Paci et al., 2007; Rand et al., 1999), quality of movement (Park et al., 2008), and performance in activities of daily living (Desrosiers et al., 2002; Morris et al., 2012). Patient populations beyond stroke survivors deal with proprioceptive deficits, including individuals with Parkinson's Disease, traumatic brain injury, and large-fiber sensory neuropathy. In addition, our proprioceptive capacities decline naturally as we age (Adamo et al., 2007; Ribeiro & Oliveira, 2007; Shaffer & Harrison, 2007). This positions proprioception as a promising subject for patient-focused research, with a foreseeable potential to drive improvements in rehabilitation practice.

The field will need to make large strides to better establish our basic understanding of proprioception and that will include addressing the current state of proprioceptive measurement. Here we address some of the issues with the current state of measurement as a preface to introducing a novel measure of upper-limb position sense, the Full Upper-Limb Posture Matching (FULPM) task. We designed this task to address current measurement concerns and, hopefully in doing so, provide a measure that will better inform our understanding of patients' deficits as they relate to clinically relevant upper-limb function.

Our bodily sense is derived in part from afferent signals from receptor organs in our muscles, tendons, and skin—known as proprioceptors (Evarts, 1981; Proske & Gandevia, 2012, 2018; John C Rothwell, 1987; Sherrington, 1907, 1909; Tuthill & Azim, 2018), though proprioception also relies on sources of information such as ongoing motor commands and their predicted sensory outcomes to estimate the current state of our body (often referred to as body "estimates" or "representations").

In practice, the term "proprioception" is most often used to describe position sense, with the term "kinesthesia" referring specifically to our sense of movement (Stillman, 2002), though by definition proprioception encompasses all of the bodily senses mentioned. Unsurprisingly, there are instances of misuse, such as kinesthesia being used to describe sense of heaviness (Fleishman & Rich, 1963). Part of this confusion may be attributed to a historical indistinction between position and movement sense. We have a poor understanding of how movement sense and position sense differ (Proske & Gandevia, 2012), including the neural substrates involved in each and when (and how) they are utilized in upper-limb action. Yet, most modalities of proprioception, including position and movement sense, appear to map onto meaningful outcomes (Meyer et al., 2014).

Proprioceptive information is often updated and utilized subconsciously, without noticeable effort. This could be because, unlike the eye, ear, or even tactile sensations, proprioceptive modalities are not easily attributable to one sensation. Proprioceptive sensation is distributed throughout the body; there isn't a localized central organ such as an eye or nose. We most acutely "feel" the sensations which subvert expectations (Proske & Gandevia, 2012, 2018), and proprioceptive signals are often predictable: our nervous system usually *knows* that movements are forthcoming and anticipates the somatosensory repercussions. Of course, much of the processing of other sensory modalities, such as vision, functions outside of conscious awareness. Whatever the explanation may be, the potential disconnects between proprioceptive perception and the unconscious proprioceptive information actionable in motor planning and execution is a serious concern that researchers have little power to address. There is evidence that proprioceptive information regarding limb configuration is available to plan reaching trajectories even when the same information isn't available to correct for limb drift, a phenomena which occurs when performing a repeated reaching task without vision (reach out to point A and back to point B, repeatedly)(Patterson et al., 2017). If accurate proprioceptive information is available to certain unconscious processes of motor planning and execution and not others, it seems plausible that a disconnect between perception and sensation may exist as well.

Measures of proprioception used in clinical and research settings invariably assess proprioceptive perceptions: they rely on subjective report. However, reliance on measures of proprioceptive perception is, for the time being, a practical necessity. It will take a great deal of further research to establish alternative means to measure proprioceptive sensations (or proxies thereof) and, importantly, whether they offer additional value. Despite these concerns, existing measures of proprioceptive perception have repeatedly been shown to be important predictors of motor learning outcomes in healthy and patient populations (Fleishman & Rich, 1963; Vidoni & Boyd, 2008, 2009) as well as predictors of numerous outcomes of clinical importance such as functional independence among stroke survivors (Meyer et al., 2014).

The link between proprioceptive perception and various outcomes (upper-limb function, quality of movement, and engagement in activities of daily living) seems to be a reliable phenomenon despite major variability among measures used. Taking this into account, alongside the prevalence of upper-limb proprioceptive deficits in stroke, proprioceptive deficits should be a prime focus in stroke rehabilitation research. Most studies report similar statistics on the prevalence of upper-limb proprioceptive deficit in stroke survivors, usually citing the same few papers which rely on one of the most common approaches of measuring proprioception, joint angle matching (a measure of position sense). They report that between 50-60% of stroke survivors live with proprioceptive deficits (L. M. Carey et al., 1996; LM Carey et al., 1993; Findlater & Dukelow, 2016), though it has been argued that rates may be much higher depending on which measure is used and the threshold chosen for determining whether a score is normal or represents impairment (Connell et al., 2008).

Typically, proprioceptive measures of position and/or movement sense fall into two categories: a) assessment of joint-angle or movement at an isolated joint (e.g., index finger, wrist, elbow, or shoulder), or b) assessment of effector endpoint position (e.g., the tip of the index finger).

A category “a” measure might have the subject (eyes closed/blinded) flex/extend their left arm at the elbow to match the ongoing flexion/extension of their right arm as it is passively moved by a researcher or robot (test of movement sense). Alternatively, the subject may have to match the left arm joint-angle to their current right arm joint-angle, after it had been passively positioned by the researcher/robot (test of position sense).

A category “b” measure might have the subject (eyes closed/blinded) touch a body part with their right arm after it has been passively positioned by a researcher/clinician. Or the subject (limbs obscured and gripping the handles of a planar robot) must match the end position of their left limb to the end position of the right arm; they could be required to match the current position of the right arm after it was passively moved by the robot (position sense) or the ongoing movement of the right arm (movement sense).

Understandably, approaches used in research most often strive to isolate features of proprioception, though rarely look across multiple features in a single study (e.g., multiple joints or proprioceptive modalities); there is likely a pragmatic explanation: thorough somatosensory assessments are time consuming, which is especially limiting when working with stroke survivors. Additionally, there are no “gold-standards” in proprioception research. No single measure, or even set of measures, has been adopted as a research standard. Among the many measures that are routinely used, often standardized scores have not been established making it difficult to determine just how many stroke survivors show impaired proprioceptive capacities (Findlater & Dukelow, 2016). Though, standardized scores for healthy individuals and stroke survivors alone wouldn’t tell us whether a score was clinically relevant; scores would need to be associated with outcomes such as limb function or functional independence.

Proprioceptive measures unique to research have one major advantage over clinical assessments, they can detect subtle differences in proprioceptive capacity/deficit. Planar robots measure movement with immense accuracy and even manual measurement of joint angles using a goniometer provides an assessment of error that is continuous and accurate when used diligently. In clinical assessments, outcomes are assigned scores based on performance. These scores reflect a categorical/qualitative assessment of deficit. For example, the Finger-Nose task is a commonly used clinical assessment where the subject (eyes closed) must touch the tip of their nose with the tip of their index finger after the limb has been passively positioned by the clinician; performance is rated on a 3-point scale (0=couldn't accomplish, 1=could accomplish with some searching, 3=could accomplish without searching). To provide an additional example, the Nottingham Assessment of Somatosensations (NSA ; Lincoln, Jackson, & Adams, 1998) has the administrator adjust the angle of an isolated joint up or down, for example, they might move the index finger so that the metacarpophalangeal joint rotates in isolation. Once the administrator brings the index finger to rest, the subject must mirror the movement with their opposite finger. They are given points based on varied aspects of the performance (0=no appreciation of movement; 1=appreciates movement is taking place, but moves in wrong direction; 2=patient moves in the correct direction, but their final angle does not match the moved joint within 10 degrees; 3=accurately mirrors the movement within 10 degrees). While this assessment judges a wider array of proprioceptive senses (movement and position), the score provides a rough depiction of the patient's deficit. In defense of clinical assessments, it is a necessity that they be brief, and a rough depiction of a patient's deficits may be sufficient in deciding whether the patient will return home or requires therapy. However, clinical assessments are reported in research, which poses the risk of underestimating the prevalence of deficit as well as the importance of proprioception in predicting outcomes.

Upper-limb measures usually target the index finger metacarpophalangeal joint, wrist, or elbow, with some looking at the shoulder (Findlater & Dukelow, 2016; Meyer et al., 2014). One reason to suspect that new measures could improve upon these traditional approaches is that proprioception is crucial in multi-joint synchronization (R. Sainburg & Ghilardi, 1995; R. Sainburg et al., 1993) which is required for most any upper-limb actions including basic reaching and transport. While some studies do take measurements across multiple joints, they take each serially, in isolation. We hypothesize that measures which include simultaneous multi-joint positioning may offer improved predictive value over these more restricted measures.

Measurement of movement sense in research is most often accomplished using planar robots or similar machines, which allow a subject's arm to be moved precisely and predictably and with less worry of experimental confounds (Dukelow et al., 2010; Findlater & Dukelow, 2016; Scott & Dukelow, 2011; Semrau et al., 2013). These approaches typically assess perception of the limb end position relative to a reference position. For example, is the position of the tip of the index finger further to the right or the left of where it had been when initially positioned at the reference (Wong, Wilson, & Gribble, 2011). By addressing effector end point position, such approaches assess multi-joint perception.

Despite definite benefits in research settings, planar robots present other restrictions: all movements take place on a 2D plane and often within a restricted workspace. There are some robotic solutions offering 3D movement, though still with restrictions such as a limited workspace and in both cases extreme cost, complexity, and time costs can be major limiting factors both in terms of clinical use and even research use; they also prevent assessment of complex actions, such as grasping or tool use. Past research suggests that the space where proprioceptive training and testing occurs is crucially important (Wong et al., 2011). In their study, healthy adults completed a measure of "proprioceptive acuity" using a planar robot; this measure was taken before and after a motor learning task. The measure of proprioception had subjects' arms positioned in the center of a 10cmx10cm area; vision of the limb was obscured. The robot would then passively move their arm to the right or left and then back to a position displaced slightly to the right or left of the reference. Subjects then made a judgement whether they were to the right or left of the reference position. During the motor learning task, subjects were required to rapidly move the robot arm to the position of a target (5mm circle) while vision of their limb was obscured. Whenever they moved within 2mm of the target it would relocate to a pseudorandom position within a 10cmx10cm area; time to reach the target was measured for each of these trials (400 trials in total). Participants performed the motor learning task either in the same 10x10 space as the proprioceptive "acuity" task, or in a similar sized space displaced 25cm to the right. They found that participants proprioceptive capacities improved after the motor learning task, though only if they performed the task in the same 10cmx10cm area as the proprioception assessment. Such restrictions on the space where testing is conducted (size of space and dimensions allowed) may limit the predictive value of measures because the sort of upper-limb actions we are interested in require movement in a large 3D space, i.e., the full extent of peripersonal space we commonly transverse as we interact with the world.

The addressed shortcomings in current proprioceptive measures prompted the development of our novel measure, the Full Upper-Limb Posture Matching task (FULPM). The most notable features of the FULPM include: 1) assessing perception across multiple upper-limb joints (wrist, elbow, and shoulder) concurrently, 2) assessing full-limb postures: postures that more closely match those that would be used in skilled upper-limb action (i.e., reaching, transport, manipulation), and 3) assessing perception of postures in 3D space, allowing full range of motion in posture formation.

Validating novel measures typically relies on one or more existing and validated measures (gold-standards). Measurement development can become tricky when entering uncharted territory or in our case, when a multitude of measures of questionable or highly specific merit exist without a clear standard. On top of detailing our novel measure, we present preliminary results comparing FULPM performance across three groups: young healthy controls, older healthy controls, and stroke survivors. This helps to show that the FULPM Task can assess proprioception across a wide range of proprioceptive capacities without running into floor or ceiling effects, which is a problem with many clinical measures of proprioception, which are only valid in more acute cases of proprioceptive deficit. Among stroke patients, we compared the FULPM task against four traditional measures of proprioception used in clinical settings and patient-centered research. Lastly, we compared patient and non-patient FULPM task performance with a commonly used motor assessment, the Box and Block task; the motor task is performed both with full visual feedback (lights on) as well as in reduced visual feedback conditions (lights off).

We hypothesize the following results: 1) stroke survivors with significant unilateral deficits will show significantly greater degradation of motor performance (Box and Block) in the more affected limb when performing in the absence of vision, and 2) older healthy adults FULPM performance will be significantly worse than younger controls.

2.1 Methods

2.1.1 Subjects

13 young healthy controls (ages 24-27, M=24.6), 5 older healthy controls (ages 48-65, M=57.6), and 5 mild stroke patients (52-73, M=61.6) were recruited for this study. Control participants primarily represent students and members of the medical research and clinical community at

Washington University School of Medicine. Young controls had to fall between the ages of 18 and 44. Older controls had to be 45 years or older. The patients were recruited from a local outpatient rehab center, through referral from area clinicians, and through the Stroke Management and Rehabilitation Team (SMART) Stroke Registry, which prospectively collects data from medicine, radiology and rehabilitation on approximately 30,000 stroke patients admitted to Barnes-Jewish Hospital (St. Louis, MO). Potential participants were identified as having “mild” sensorimotor symptoms based on their records at the time of hospital discharge or through clinicians’ judgement. For stroke patients, 7 individuals were screened and two did not qualify.

All patient and control participants gave informed consent in accordance with local ethics committee recommendations.

Stroke Patient Inclusion & Exclusion. We did not restrict recruitment based on age or time since stroke incident. Potential participants were excluded if they showed: a) signs of cognitive deficit as assessed by a score <=25 on the Montreal Cognitive Assessment (MoCA; Julayanont et al., 2015), b) signs of visual-spatial neglect as determined by a score >= 44 on the Star Cancellation Test, c) if they did not have normal or corrected to normal visual acuity as determined by the Lighthouse Near Acuity Test, d) impairment to range of motion, and e) signs of fatigue or weakness of the limb. Range of motion, fatigue, and weakness were assessed through participant interview and ultimately a decision was made based on whether the experimenter judged that a deficit would interfere with their ability to form and maintain upper-limb postures. One participant was excluded based on cognitive deficit and another due to a non-stroke diagnosis (Julayanont et al., 2015).

2.1.2 FULPM Task

FULPM Design and Procedure.

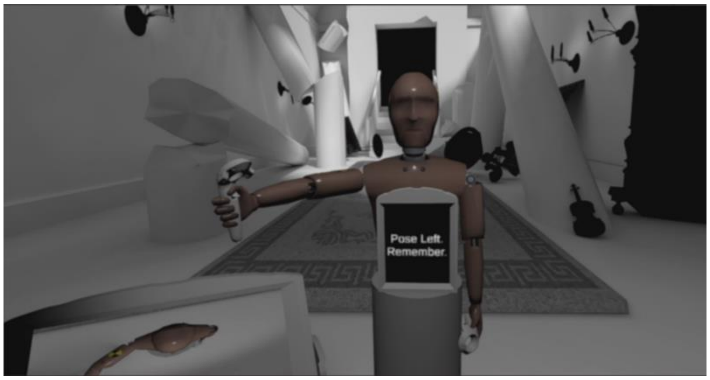

Figure 2.1. The virtual environment seen through the virtual reality headset. The 3D model ("dummy") is presenting a posture for the participant to mirror. On the bottom left of the image is a top down view of the dummy adding an extra point of view for the participant.

The FULPM task uses position trackers fixed to multiple points on each upper-limb to measure the spatial position of limb segments (palm, forearm, and upper-arm) while participants assume postures. To be clear, unlike most measures of position sense, we are not assessing joint angles; we are assessing the 3D positioning of limb segments. The FULPM task is performed entirely while seated to ensure patient safety. A head-mounted virtual-reality system is used to occlude vision of participants own limbs while providing a visual task cue. The visual cue is a 3D model of a humanoid figure positioned directly in front of and facing towards the participant. The model postures one of its limbs as an example posture, and the participant must approximate the posture with their own limb: this posture will be the reference posture (Figure 2.1). Participants are then required to match the posturing of the limb being tested to either the current posture of the contralateral limb (reference limb) or a previous posture of the same limb being tested (reference limb is the test limb). A single score is derived for each trial and represents the average spatial disparity (position error) between the limb segments of the reference limb and the test limb. Both limbs are tested under all condition.

The FULPM task includes two independent variables, each with two levels. The first variable is the nature of the reference limb which includes 1) the contralateral limb condition (contra), and

2) the memory condition (the same limb is used as reference and for testing). The second variable is reference limb positioning and pertains to how the reference limb is moved into position, either 1) actively (by the participant) or, 2) passively (by the experimenter). The active movement conditions allow participants to incorporate motor commands into their estimates of limb position, something that is typically available in everyday situations, though theoretically could be used to reproduce postures with the tested limb by repeating the motor commands as opposed to relying solely on sense of position. In the passive condition the motor command is removed. The task is broken up into the following four blocks (Figure 2.2):

Block 1	**Block 2**	**Block 3**	**Block 4**
Contralateral Reference	Contralateral Reference	Memory Reference	Memory Reference
Active Positioning	Passive Positioning	Active Positioning	Passive Positioning
4 Left + 4 Right = 8 Trials	4 Left + 4 Right = 8 Trials	4 Left + 4 Right = 8 Trials	4 Left + 4 Right = 8Trials

Figure 2.2. Design of the FULPM Task blocks. The presentation order of left limb and right limb trials within a block is randomized in real time by the FULPM software.

In each block a total of 8 trials are collected: 4 for the left limb and 4 for the right limb. The presentation order of left limb and right limb trials within a block is randomized in real time by the FULPM software. A step-by-step illustration of the FULPM task trial procedures can be seen in Fig. 2.3A (contralateral reference) and 2.3B (memory reference).

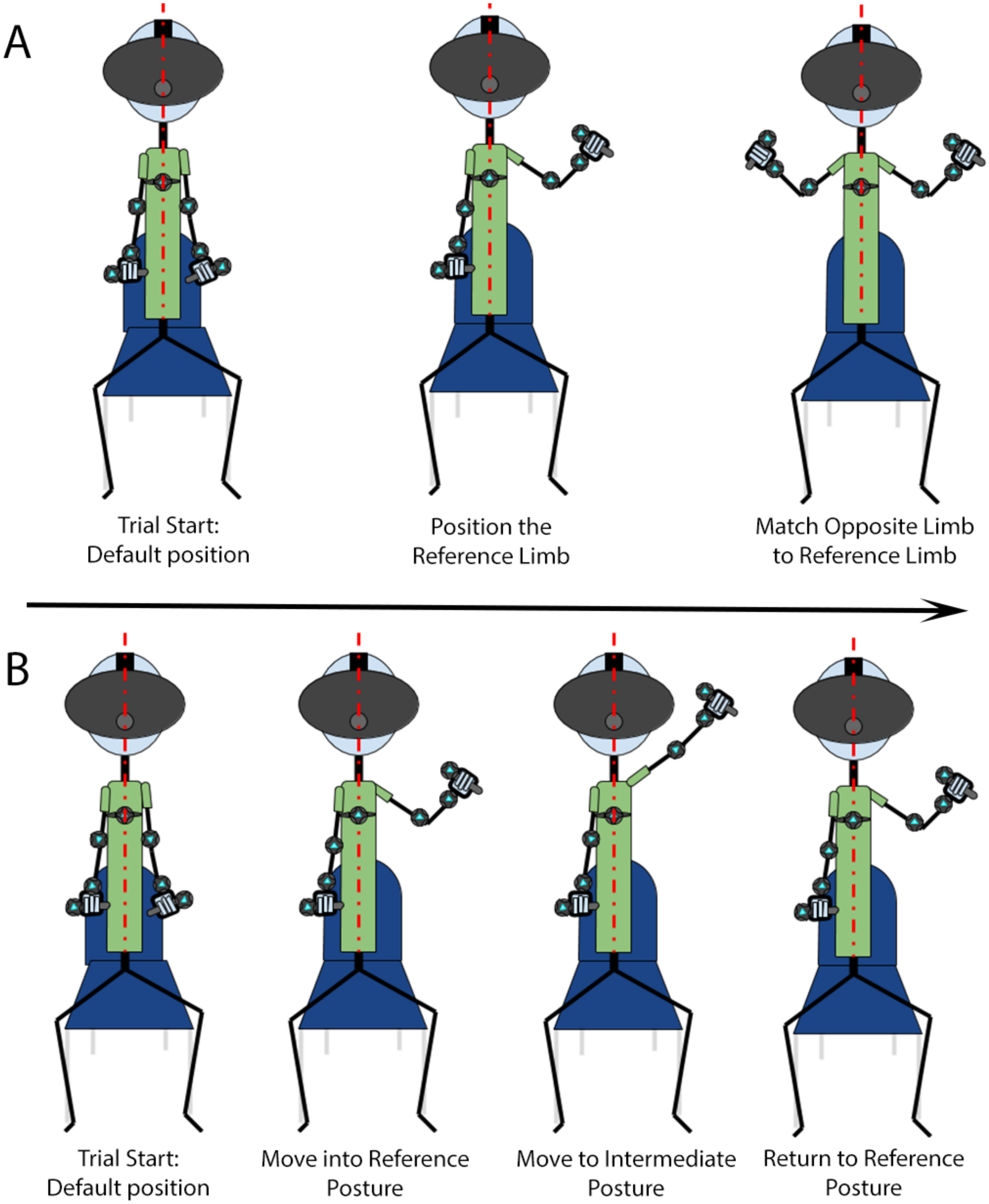

Figure 2.3. Illustration of FULPM reference conditions. A: The contralateral reference condition. B: The memory reference condition.

VR and Position Tracking Equipment. The FULPM task was developed using the HTC Vive, a head-mounted VR system developed by HTC (New Taipei City, Taiwan) and Valve Corporation (Seattle, WA). The headset uses "room scale" tracking technology, allowing the user to move in 3D space and use motion-tracked handheld controllers and body mounted tracking sensors (sold separately) to interact with the environment. The body mounted sensors are the commercially available Vive Trackers (version 2.0). Two external wall mounted sensors are used to track the 3D position and rotation of the headset, controllers, and body trackers. The HTC Vive system has impressive spatial accuracy given its cost. The headset appears to have sub-centimeter accuracy, which was validated using a highly accurate Vicon optical position tracking system (Veen, Bordeleau, Pidcoe, France, & Thomas, 2019). The Vive Trackers have sub-centimeter accuracy for positioning when held relatively still, though accuracy was found to drop during movement (Borges, Symington, Coltin, Smith, & Ventura, 2018); the FULPM only assesses 3D positioning of the headset, controllers, and trackers during periods where the participants are holding postures (no movement). Fig. 2.4 shows a participant equipped with trackers, headset, and controllers.

Figure 2.4. A subject donning the Vive trackers on the limbs (upper arm and forearm) and chest with Vive controllers in hand.

FULPM Software. The FULPM task software was developed in-house using the Unity Engine (UnityTechnologies, 2020). Unity Engine is a multipurpose 3D engine and editor commonly used in VR game and software development. 3D modeling and design was also performed in Autodesk Maya (Autodesk & INC., 2020).

2.1.3 Traditional clinical measures of proprioception

Four measures of proprioception commonly used in clinical and patient-focused research were chosen. Several considerations guided our selection of measures: 1) an equal representation of measures used in the clinic and in research, 2) limited time demands in part because both limbs will be tested and because of our next consideration, 3) among measures where single-joints are isolated, it is possible and makes sense to measure at multiple upper-limb joints, specifically extension and flexion at the index finger metacarpophalangeal joint, wrist, elbow, shoulder.

Thumb Finding Test. A commonly used test used in the clinic. The experimenter positions one of the participants upper limbs while the participant assumes a “thumbs up” type hand posture. The participant is then asked to touch the thumb of the positioned limb with their contralateral thumb and forefinger (akin to a pincer grasp) while their eyes are closed (Garraway et al., 1976). A score is produced based on how they perform in finding the positioned thumb without vision. The task is repeated three times for each limb, alternating between left and right.

Finger-Nose Test. Another commonly used test in clinical settings. The experimenter positions one of the participants limbs while the participants form an index pointing position with the positioned hand. The participant is then asked to locate and touch their nose with their index finger while their eyes are shut (Taylor & McCloskey, 1988). Outcomes are binary: whether or not the participant was able to locate their nose. The task is repeated three times per limb, alternating between left and right.

Proprioceptive Discriminations Test. A subtest of the Rivermead Assessment of Somatosensory Performance (RASP). The RASP is a quantitative assessment designed for use in stroke patient populations and is used most commonly in patient-focused research. This assessment looks at perceptions of movement and position sense at isolated joints. The experimenter moves the joint up or down six times, each time moving the joint approximately 20° and giving pause between movements for the patient to respond whether they feel movement and, if so, what direction they felt it in (Winward, Halligan, & Wade, 2002). The participant keeps their eyes shut while any joint is being tested. The experimenter takes care to move the segment of the limb so as not to provide obvious tactile cues. Scores are produced for each joint tested and consider both whether movement was detected and, if so, whether they could identify the direction of the movement. The procedure described is performed once per joint on each limb; for a single joint left and then right were tested before moving on to the next joint.

Kinaesthetic Sensations. A subtest of the Nottingham Sensory Assessment (NSA). The NSA has been used commonly in clinical trials following stroke to test various interventions. It is also used in other research as well as clinical settings (though not regularly). This assessment looks at perceptions of movement and position sense at isolated joints. The limb on the affected side of the body is supported and moved by the experimenter in various directions but movement is only at one joint at a time. The patient is asked to mirror the change of movement with the other limb (Lincoln et al., 1998). The participant keeps their eyes shut while a joint is being tested. The experimenter takes care to move the segment of the limb so as not to provide obvious tactile cues. Scores are produced based on whether the participant accurately perceived the movement, its direction, and reproduce the tested limbs positioning. The task is repeated three times for each joint, alternating between left and right within a joint and collecting all data for a joint before moving to the next.

2.1.4 Motor task

The Box and Block test was used as our primary motor assessment. The Box and Block Test is an assessment of manual dexterity and gross arm movement that has been widely used in rehabilitation research as well as clinical settings (Mathiowetz, Volland, Kashman, & Weber, 1985). We chose this task for several reasons, including 1) it is simple to administer and does not take much time, 2) it is a widely used measure used in rehabilitation research including work with stroke patient populations, and 3) it is unlikely to run into floor or ceiling effects.

The standard procedure for the Box and Block Test was followed. A test box with 150 blocks and a partition in the middle was placed lengthwise along the edge of a standard-height table. The patient was seated on a standard height chair facing the box. 150 blocks are placed in the compartment of the test box on the side of the limb that will be tested. When testing began, the patient would grasp one block at a time with the hand, transporting the block over the partition, and releasing it into the opposite compartment. The patient would continue doing this for one minute. The procedure would then be repeated with the nondominant hand. After testing, the experimenter counted the blocks. If a patient transported two or more blocks at the same time, this is noted, and the number subtracted from the total. No penalty was made if the subjects transported any blocks across the partition and the blocks bounced from the box to the floor or table. The task can be seen in Figure 2.5 (Mathiowetz et al., 1985).

Figure 2.5. A participant performing the Box and Block task.

Following the standard protocol described above, the procedure was repeated in a partial visual feedback (PF) condition. All lights in the testing room were turned off and the test was administered in the dark. This condition was always administered following the standard protocol so that participants could become accustomed to the task; this alleviates the concern that had participants started with the PF condition first then their poor performance could be attributable to familiarity with the task as opposed to a difficulty performing when unable to rely on visual feedback of the limb. Thus, we have two feedback conditions: 1) full feedback (FF), and 2) partial feedback (PF).

2.1.5 Study procedure

All testing took place within a single test session in a research laboratory setting, during the same visit as the study in Chapter 3. After providing informed consent participants underwent screening to determine whether they qualified to participate. If they qualified and still desired to participate the testing session began. Two stroke patients did not qualify to participate in the study.

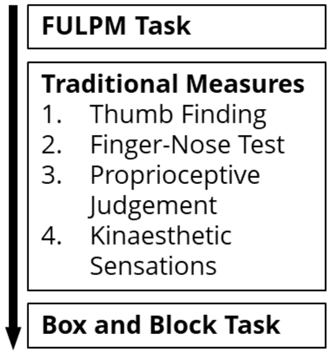

Figure 2.6. The order of procedures during a testing session for stroke patient participants.

Figure 2.6 depicts the order tests were administered for stroke patient participants. Both control groups did not complete the traditional measures of proprioception, since those tests were all designed for clinical use or patient-focused research, and thus by design all healthy adults perform at ceiling.

2.2 Analyses

All data preprocessing and analyses was performed in C# (Microsoft Corporation, 2000-2020) and R (Team, 2016).

Multi-factor significance testing was conducted using linear mixed models (fit using restricted maximum likelihood [REML]). Mixed models were implemented using the ‘lme4’ package for R. Participant “ID” was included as a random effect to account for repeat measurements across limb (left/right) and feedback condition (FF/PF) within subjects. Below is an example model using the lme4 package which tests the main effects of ‘Group’, ‘Feedback Condition’, and ‘Limb Tested’, as well as all possible interaction effects, on our ‘DV’; “ID” is included as a random effect:

$$lmer(DV \sim Group * Feedback * \ LimbUsed + (1|ID), data = \ TestData)$$

Post-hoc testing using Tukey’s method for p-value adjustment was used to interpret significant interactions; post-hoc tests were implemented using the ‘emmeans’ package for R.

Subject mean scores were calculated per control participant per condition. Patient participants were treated as case-studies, therefor all patient data points were included. Welch’s two-sample t-tests were used for simple group comparisons; two-sample paired t-tests were used for simple within subject comparisons.

The ‘lmer’ function we used to build and test linear mixed models utilizes Satterthwaite’s method for approximating degrees of freedom (1941) and the ‘emmeans’ function we used in post-hoc testing utilizes Kenward-Roger approximation (1997). These methods of degrees of freedom approximation, as well as the REML approach to estimating variance, have been shown through simulations to produce acceptable Type 1 error rates, even in small samples (Luke, 2017). However, this is a pilot study which aims to establish the FULPM task as a measure suitable for use in healthy individuals and stroke survivors. Significance tests were conducted to identify potentially significant factors for future study. Caution should be taken in interpreting test results given small sample sizes.

Patient case-studies are handled primarily through data exploration in lieu of significance tests.

2.3 Results

Control age group has a significant impact on FULPM performance, but not motor performance.

$$lmer(FULPM\_Error \sim ControlGroup * Condition * \ LimbUsed + (1|ID))$$

On FULPM task, there was a significant main effect of age group [β=-0.67, t=3.5, p<0.001], with 45+yo group (M= 5.29, SD=3.25) performing worse than the <45yo group (M= 3.59, SD=3.34). A closer look at control performance per FULPM condition can be seen in Fig 2.7.

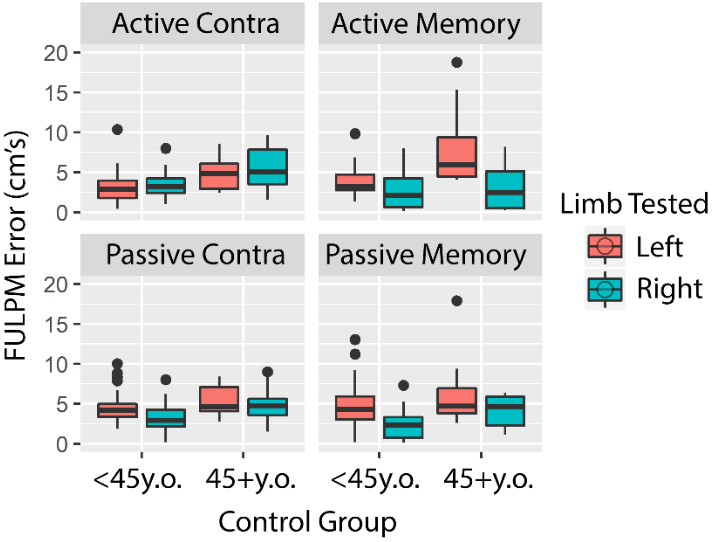

Figure 2.7. Control performance on the FULPM task across conditions and limb tested.

Motor performance—as assessed by the Box and Block task—during the FF condition (M=58, SD=11.6) was significantly greater than during the PF condition (M=43.4, SD=6.9) regardless of age group [β=6.9, t=13.3, p<0.0001]. Performance between age groups approached significance (p=0.07), with the younger group showing a trend of better performance (M=53, SD=12.9) than the older group (M=44.4, SD=6.7). There was a significant interaction effect between feedback condition and age group [β=1.2, t=2.3, p=0.02]: pairwise comparisons indicate a significant difference between the younger group in the FF condition (M=61.2, SD=12.2) and the older group in the PF condition (M=38.7, SD=3.7) [β=22.45, t=4.9, p<0.0001], which appears to be driven by a large variability in performance among younger controls during the FF condition, with many performing drastically better with visual feedback, as opposed to the expected significant decrease in performance by the older group in the PF condition.

We found a significant main effect of handedness [β=-0.78, t=-3.09, p<0.01], with the non-dominant limb performing worse (M=4.58, SD=2.95) than the dominant limb (all participants were right handed; M=3.13, SD=3.71) on the FULPM task. There was no effect of limb used on motor performance.

The differences between control age groups and between dominant and non-dominant limb, even if significant on the FULPM task, were minor relative to the error observed in patients on the FULPM task. Therefore, we have grouped the controls for subsequent comparisons against stroke patients.

The memory conditions identify significant proprioceptive impairment in the right/impaired limb.

$$lmer(FULPM\_Error \sim Reference * Movement\ *\ LimbUsed + (1|ID))$$

All patients reported impairment in their right limb. Among patients, there was a significant interaction between FULPM condition and the limb used [β=3.49, t=2.02, p<0.05], such that only the memory condition's identified a significant difference between the reported impaired/right limb and the left limb. Results for all patients per condition can be seen in Fig 2.8.

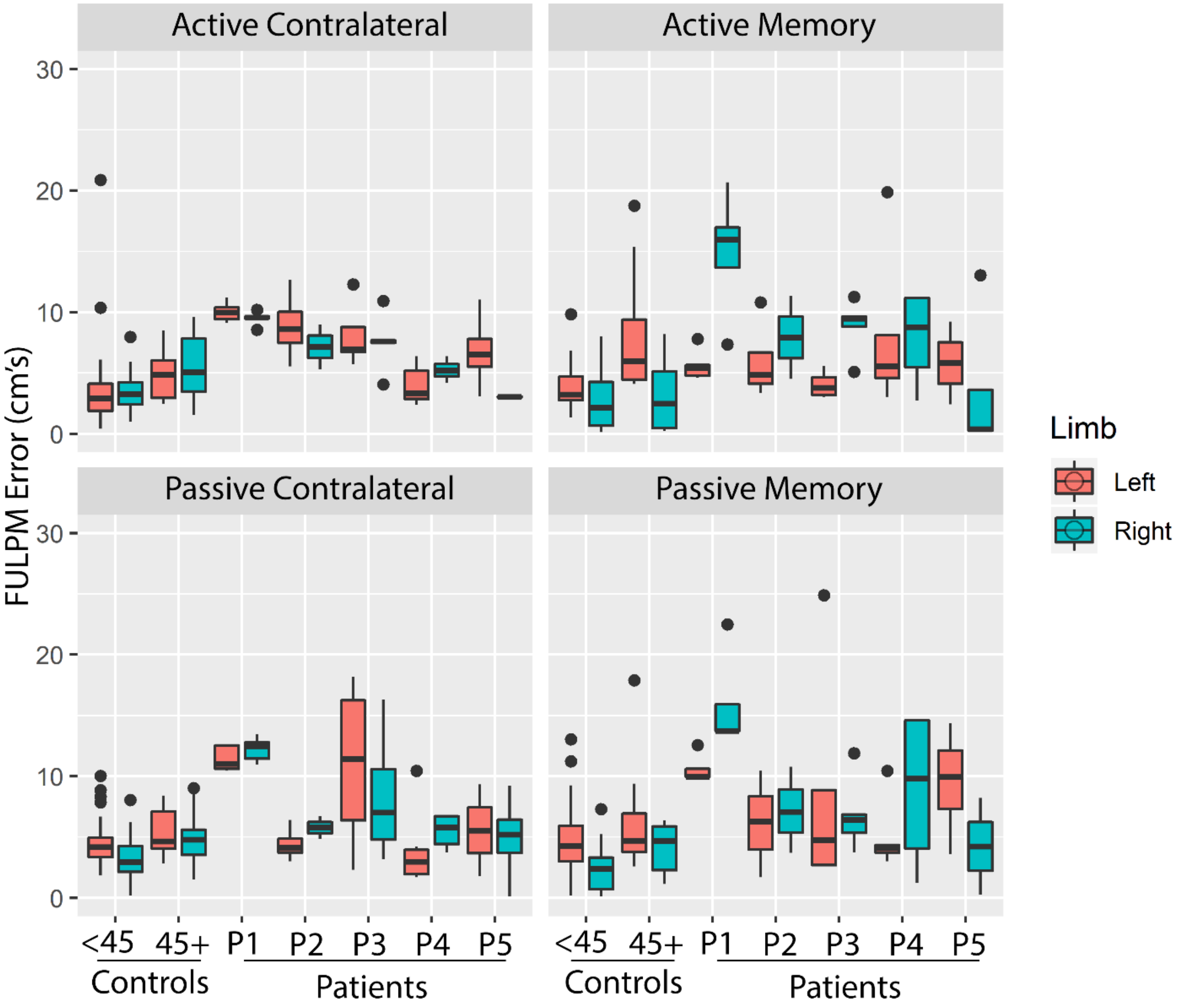

Figure 2.8. FULPM performance among controls and patients. The active memory condition (top right) shows the greatest difference in error between the reported affected and "unaffected" limb.

The difference in impairment between limbs appears to be most noticeable in the active memory condition, though due to the limited sample pairwise comparisons of three factors isn't possible. While patient 5 reported impairment of the right limb, their results show the opposite.

Patient performance on the FULPM task appears to correlate with motor performance. Given the sample size among patients, a correlation analysis between motor performance and FULPM performance wouldn't be informative. Fig 2.9 shows performance on the Box and Block task among both control groups and each patient. Among the patients that showed greater proprioceptive deficit in their right limb, their performance with the right limb appears to degrade when performing without visual feedback. Patient 5 does show a general decline in performance during the partial feedback condition, but no interaction.

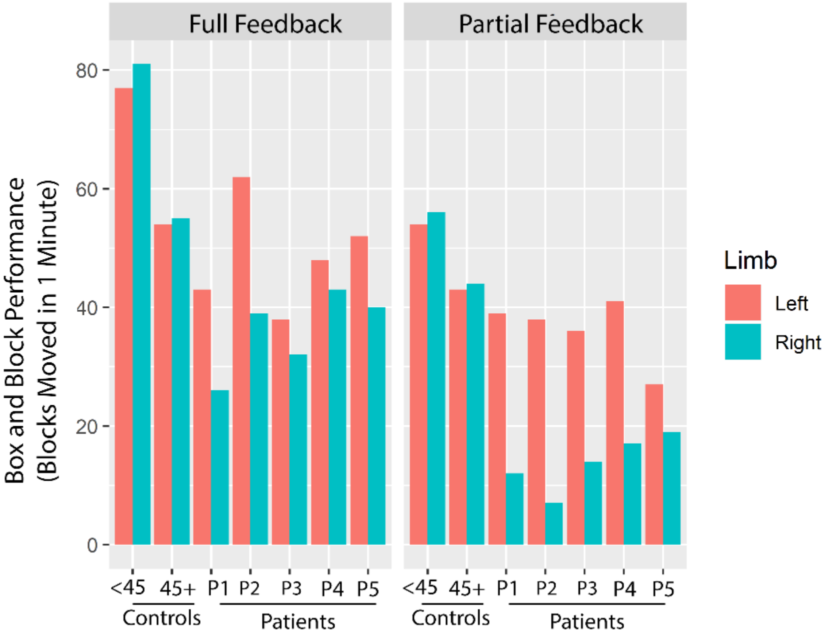

Figure 2.9. Performance on the Box and Block task across feedback conditions.

Traditional measures of proprioception are unreliable on repeat tests. The Thumb-Finding and Finger-Nose task (Tbl 1) did reflect right limb proprioceptive deficit for some patients, though performance varied across trials. Patient 5 did not show significant deficit in the right limb according to the FULPM task, though did on the Thumb-Finding and Finger-Nose task. Their performance on the Proprioceptive Discriminations assessment did not suggest deficit in the right limb (Tbl 2), whereas their performance on the Kinaesthetic Sensations assessment shows a mild deficit in the right limb. Measured deficit varied across joints in both limbs (Tbl 2

& 3). There appears to be little relation between the difference in performance of the right and left limb in the FULPM task and the traditional measures.

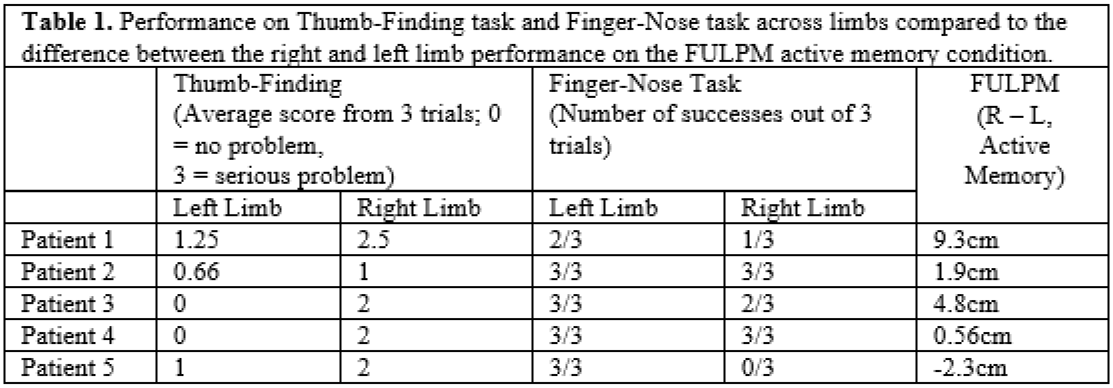

Table 1. Performance on Thumb-Finding task and Finger-Nose task across limbs compared to the difference between the right and left limb performance on the FULPM active memory condition.

	Thumb-Finding (Average score from 3 trials; 0 = no problem, 3 = serious problem)		Finger-Nose Task (Number of successes out of 3 trials)		FULPM (R – L, Active Memory)
	Left Limb	Right Limb	Left Limb	Right Limb	
Patient 1	1.25	2.5	2/3	1/3	9.3cm
Patient 2	0.66	1	3/3	3/3	1.9cm
Patient 3	0	2	3/3	2/3	4.8cm
Patient 4	0	2	3/3	3/3	0.56cm
Patient 5	1	2	3/3	0/3	-2.3cm

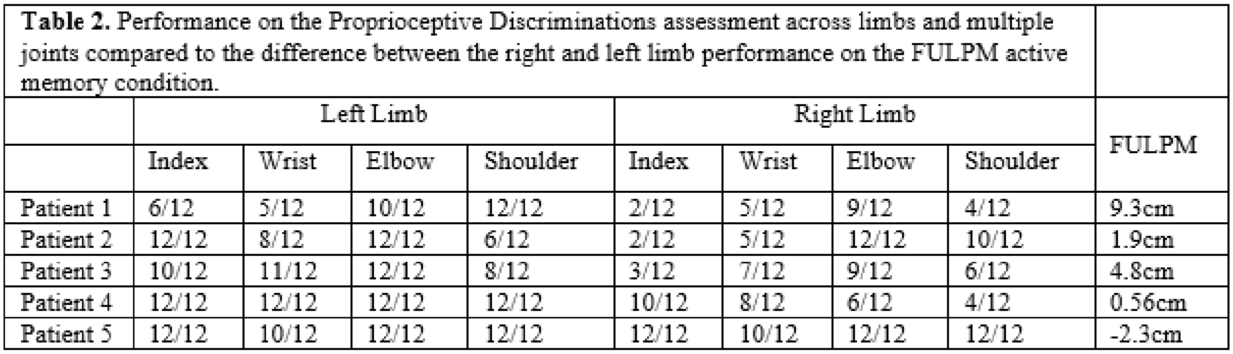

Table 2. Performance on the Proprioceptive Discriminations assessment across limbs and multiple joints compared to the difference between the right and left limb performance on the FULPM active memory condition.

	Left Limb				Right Limb				FULPM
	Index	Wrist	Elbow	Shoulder	Index	Wrist	Elbow	Shoulder	
Patient 1	6/12	5/12	10/12	12/12	2/12	5/12	9/12	4/12	9.3cm
Patient 2	12/12	8/12	12/12	6/12	2/12	5/12	12/12	10/12	1.9cm
Patient 3	10/12	11/12	12/12	8/12	3/12	7/12	9/12	6/12	4.8cm
Patient 4	12/12	12/12	12/12	12/12	10/12	8/12	6/12	4/12	0.56cm
Patient 5	12/12	10/12	12/12	12/12	12/12	10/12	12/12	12/12	-2.3cm

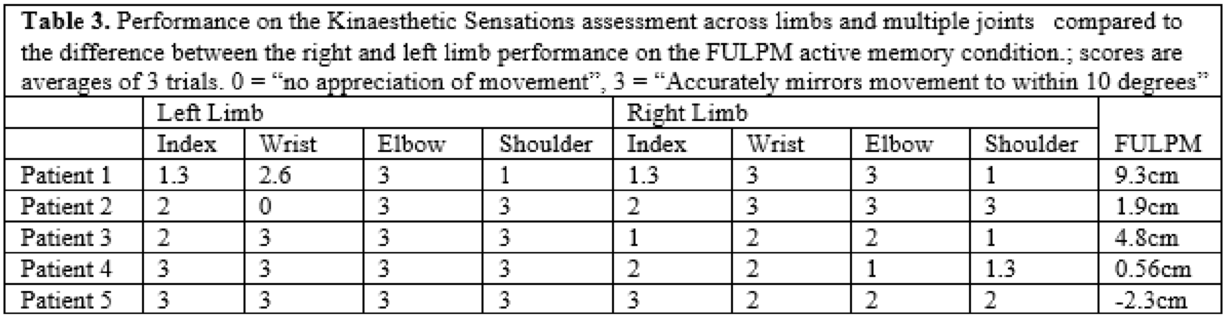

Table 3. Performance on the Kinaesthetic Sensations assessment across limbs and multiple joints compared to the difference between the right and left limb performance on the FULPM active memory condition.; scores are averages of 3 trials. 0 = "no appreciation of movement", 3 = "Accurately mirrors movement to within 10 degrees"

	Left Limb				Right Limb				FULPM
	Index	Wrist	Elbow	Shoulder	Index	Wrist	Elbow	Shoulder	
Patient 1	1.3	2.6	3	1	1.3	3	3	1	9.3cm
Patient 2	2	0	3	3	2	3	3	3	1.9cm
Patient 3	2	3	3	3	1	2	2	1	4.8cm
Patient 4	3	3	3	3	2	2	1	1.3	0.56cm
Patient 5	3	3	3	3	3	2	2	2	-2.3cm

2.4 Discussion

Proprioceptive deficits are common in stroke survivors and these deficits have been linked to important outcomes like quality of movement and functional independence. We still have much to learn about how these deficits manifest, and how it relates to clinically relevant outcomes.

Here we present the results of a preliminary study to establish the validity of our novel FULPM task.

While this is a pilot study with a small sample, we have evidence that the FULPM task can identify unilateral proprioceptive deficits and that these deficits relate to performance degradation in motor tasks when visual feedback of the limb isn't available. However, even with our sample of five patients, there is obvious variability. Patient 5, for instance, reports significant deficits in their right limb, though the FULPM task showed worse performance on their left limb. Interestingly, patient 5 did not show the increased degradation in performance on the motor task when performing without visual feedback.

In this sample the traditional measures of proprioception were unreliable and did not reflect the deficit seen on the FULPM task. While a much larger sample size would be needed to truly test the validity of the FULPM task, it seemed to perform more consistently than the traditional measures, which gave drastically different impressions of each patient's deficit.

Despite our small sample, the FULPM task was able to discern differences in proprioceptive capacity in our two control groups (<45y.o. and 45+y.o.). We did not, however, find a significant difference in motor performance between the two control groups when performing without visual feedback; instead, we found that the younger controls performed significantly better during the ff condition, though similarly to the older controls in the pf condition.

The memory condition of the FULPM identified the most drastic impairment in the affected limb. This may be due to the fact that the contralateral condition requires patients to either match their impaired limb to their unimpaired limb or match their unimpaired limb to their impaired limb reference. Because of this, the contralateral reference conditions may be removed from the task in future studies.

Further research will be needed to determine why the FULPM appeared to track proprioceptive deficit in all but one of the patient participants. In future research we will compare the FULPM to more intensive measures of proprioception used in research, such as joint angle matching or planar robot measures of movement sense. Given the disparate ratings of impairment across joints on the two traditional measures which assess joints in isolation, we will have to explore whether such variability is common using more accurate measures, like joint angle matching.

While it is difficult to draw conclusions, this study has provided several findings that will guide future research. Despite limitations, these preliminary results suggest the FULPM may be a robust measure of proprioceptive deficit that can be employed across the spectrum of proprioceptive capacity and deficit.

In Chapter 3, the results from the memory condition of the FULPM task are compared against reaching performance in similar visual feedback conditions.

Chapter 3: The importance of vision in reach control and performance among stroke survivors with proprioceptive deficits.

Proprioception – our sensations and perceptions of bodily position, movement, and effort – is a critical component in skilled upper-limb action. Researchers are still working to understand the intricate relationship our bodily senses play in upper-limb function and performance, and likewise, we still have much to learn about the impact proprioceptive deficits can have on function and recovery. The discoveries we make in healthy or patient populations bolster our understanding of the other, and both will be important in eventually developing effective rehabilitation strategies. For example, the strategies stroke patients with proprioceptive deficits use to compensate can inform how proprioception is typically utilized in motor control and which activities proprioception is most important in. In this chapter we aid in this effort by probing how reaching performance in stroke survivors is mediated by both the degree of proprioceptive deficit and the availability of visual feedback of the limb during action execution.

Proprioception is crucial in acquiring and improving motor skills. For example, reduced proprioceptive capacity in stroke survivors is predictive of poorer motor learning outcomes after upper-limb training ("capacity" reflecting what an individual can accomplish in a controlled environment such as a lab); and in healthy young adults, proprioceptive capacity predicts the magnitude of their post-training, ceiling-level performance on a upper-limb task (Fleishman & Rich, 1963; Vidoni & Boyd, 2008). Proprioception is important in the control and regulation of coordinated movements (Findlater & Dukelow, 2016; Fleishman & Rich, 1963; Hughes et al., 2015; Marc Jeannerod, 1988; Sarlegna et al., 2006; Scheidt & Stoeckmann, 2007; Vidoni & Boyd, 2009) and action planning (Ghez et al., 1995b; Rossetti, Stelmach, Desmurget, Prablanc, & Jeannerod, 1994; Sarlegna & Sainburg, 2009). Patients with targeted loss of proprioceptive and somatosensory afferents due large-fiber sensory neuropathy without impairment to motor systems have slow and clumsy movements (Ghez et al., 1995b; Gordon et al., 1995b; Messier et al., 2003; J. Rothwell et al., 1982; Sarlegna et al., 2006). Given that our bodily senses play an important role in motor learning and action planning and execution, it may not be a surprise that proprioceptive deficits, such as are commonly seen in stroke survivors, can have major impacts on upper-limb quality of movement and function (Paci et al., 2007; Park et al., 2008; Rand et al., 1999) and on patients performance in activities of daily living (Desrosiers et al., 2002; Fullerton et al., 1988; Prescott et al., 1982).

A least 50-60% of stroke survivors live with proprioceptive deficits, (LM Carey et al., 1993; Findlater & Dukelow, 2016; Prescott et al., 1982), which represents over three million individuals in the United States alone (Benjamin et al., 2017). And, it has been suggested that these estimates may be too conservative, meaning many more patients may be living with significant proprioceptive deficits (Connell et al., 2008); this uncertainty may be in part due to the state of proprioception measurement, which was discussed in Chapter 3. Therefore, it is important to assess how patients are affected across the spectrum of deficit severity.

We often reach and grasp objects in the absence of vision of the hand. For example, we often jump back and forth between our keyboard and mouse without having to look. Research indicates that the removal of such visual feedback has only modest effects on timing and precision in healthy adults (Goodale et al., 1986; Prablanc, Pélisson, & Goodale, 1986;

Reichenbach et al., 2009). Though it isn't always the case that vision has minimal effect on upper-limb performance: in simple or common tasks, we rarely visually monitor our bodies (Johansson et al., 2001), though this is not the case for novel tasks. For example, a study found correlations between visual monitoring behavior and expertise in surgeons, with novice surgeons occasionally monitoring their hands and tools (as well as making more errors) while expert surgeons rarely focused on their bodies or tools, presumably relying on non-visual mechanisms such as proprioception and feedforward prediction (Law et al., 2004).

Individuals with proprioceptive impairments often compensate for those deficits by using visual feedback to monitor their limbs in action; this monitoring occurs even in simple tasks such as walking or reaching to grasp objects. This has been observed in cases of large fiber neuropathy (Ghez et al., 1995b; McNeill, Quaeghebeur, & Duncan, 2010) as well as in stroke (Semrau et al., 2018). Visual monitoring can result in immediate improved performance but is associated with suboptimal movement patterns (R. Sainburg et al., 1993) and based on work in healthy subjects, which shows proprioceptive capacity to be crucial in skill mastery, we might expect proprioceptive deficit to hinder recovery (Fleishman & Rich, 1963). In fact, the degree of proprioceptive deficits in stroke predicts motor learning outcomes (Vidoni & Boyd, 2009). Visual monitoring is inefficient and taxing relative to non-visual strategies (Frédéric Crevecoeur & Scott, 2014; Gentilucci, Toni, Chieffi, & Pavesi, 1994; Scott, 2016), introduces delays (relative to proprioception) that impair rapid movement correction (Scott, 2016) and simply cannot compensate fully for proprioceptive deficits (Semrau et al., 2018).

In this study we utilized two virtual reality-based reaching tasks to identify the relationship between task performance, proprioceptive deficit, and the availability of visual feedback among stroke survivors. We compared patient performance to the performance of healthy young controls and healthy older controls. We predicted that patients will perform worse when vision of the hand is denied compared to controls, that performance degradation would be greatest in their most impaired limb, and that this effect would be strongest in our virtual reality task which required greater online control of movement as opposed to more simple ballistic reaching movements.

3.1 Methods

3.1.1 Subjects

13 young healthy controls (ages 24-27, M=24.6), 5 older healthy controls (ages 48-65, M=57.6), and 5 mild stroke patients (52-73, M=61.6) were recruited for this study. Control participants primarily represent students and members of the medical research and clinical community at Washington University School of Medicine. Young controls had to fall between the ages of 18 and 44. Older controls had to be 45 years or older. The patients were recruited from a local outpatient rehab center, through referral from area clinicians, and through the Stroke Management and Rehabilitation Team (SMART) Stroke Registry, which prospectively collects data from medicine, radiology and rehabilitation on approximately 30,000 stroke patients admitted to Barnes-Jewish Hospital (St. Louis, MO). Potential participants were identified as having “mild” symptoms based on their records at the time of hospital discharge or through clinicians’ judgement. For stroke patients, 7 individuals were screened and two did not qualify. All patients reported unilateral impairment of their right limb.

All patient and control participants gave informed consent in accordance with local ethics committee recommendations.

Stroke Patient Inclusion & Exclusion. We did not restrict recruitment based on age or time since stroke incident. Potential participants were excluded if they showed: a) signs of cognitive deficit as assessed by a score <=25 on the Montreal Cognitive Assessment) (MoCA; Julayanont et al., 2015), b) signs of visual-spatial neglect as determined by a score >= 44 on the Star Cancellation Test, c) if they did not have normal or corrected to normal visual acuity as determined by the Lighthouse Near Acuity Test, d) impairment to range of motion, and e) signs of fatigue or weakness of the limb. Range of motion, fatigue, and weakness were assessed through participant interview and ultimately a decision was made based on whether the experimenter judged that a deficit would interfere with their ability to form and maintain upper-limb postures. One participant was excluded based on cognitive deficit and another due to a non-stroke diagnosis.

3.1.2 Virtual reality reaching tasks

Overview. We developed three upper-limb reaching tasks that make use of head-mounted virtual reality. The virtual reality system allowed us to track the participants hands to determine task performance, and to control visual feedback of the limb (i.e., providing or removing the 3D model of the hand). The tasks were designed to address both ballistic reaching movements (requiring few sub-movements and minimal online error correction) and highly controlled feedback-driven movements (requiring many sub-movements and online error correction).

Virtual Reality Equipment. We use the HTC Vive for our VR-based tasks, a VR system developed by HTC (New Taipei City, Taiwan) and Valve Corporation (Seattle, WA) which includes a head-mounted display (HMD). The headset uses "room scale" tracking technology, allowing the user to move in 3D space. Two external wall mounted sensors (“lighthouses”) are used to track the 3D position and rotation of the headset, controllers, and body trackers. The headset has sub-centimeter accuracy (~3mm variability) which was validated using a highly accurate Vicon optical position tracking system (Veen et al., 2019).

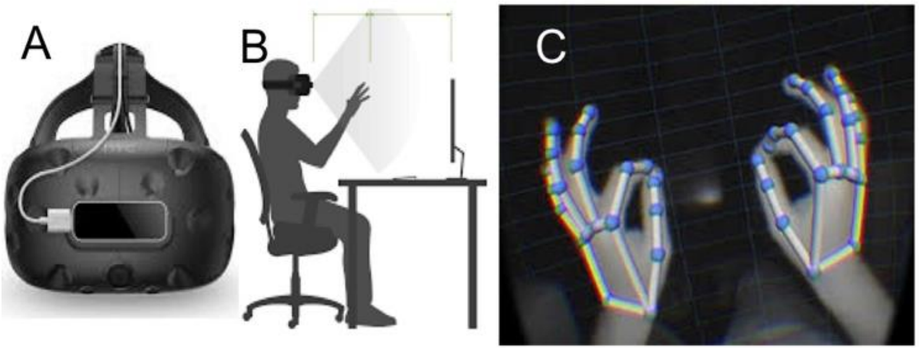

Figure 3.1. A: The hand tracking controller mounted to the face of the VR HMD, B: A characterization of the hand tracking controllers’ field of view, C: A representation of the hand model created by the hand tracking controller.

Hand Tracking Controller. Hand position is detected by the Leap Motion controller (Leap Motion, Inc, San Francisco, CA), a small USB peripheral device which is fixed to the front of the VR HMD as shown in Figure 3.1A. It uses two monochromatic IR cameras and three infrared LEDs which track a roughly hemispherical area, to a distance of about 1 meter, as illustrated in Figure 3.1B. The LEDs generate patternless IR light and the cameras record the reflected IR light at 200 frames per second. Data are sent through a USB cable to the host computer, where it is analyzed by the Leap Motion software to synthesize 3D position of multiple points throughout the hand. The overall average accuracy of the controller is 0.7 millimeters (Weichert, Bachmann, Rudak, & Fisseler, 2013).

Task Software. The reaching tasks were developed in-house using the Unity Engine (UnityTechnologies, 2020). Unity Engine is a multipurpose 3D engine and editor commonly used in VR game and software development. 3D modeling and design was also performed in Autodesk Maya (Autodesk & INC., 2020).

General Task Procedures. All tasks feature a 2x2 design: 1) visual feedback of the hand (Full-Feedback/No-Feedback), and 2) limb used (Left/Right). The Full-Feedback (ff) condition was always completed for both the Left and Right limb first, followed by the No-Feedback condition (NF) for both limbs. All tasks begin with a small starting sphere in front of the participant. During this time the participant can see the 3D model of their hand being tested. Once the participant places the tip of their index finger or center of their palm (depending on the task) within the sphere, and waits for 3 seconds, a trial is initiated. Task specific parameters, such as the location or ordering of stimuli, were constant across participants to control task difficulty.

Task 1: 3D Tracing. In the 3D Tracing task the participant begins a trial by placing the tip of their index finger in the the start sphere. Following a brief delay (a random time between 1 and 3 seconds) a 3D tubular shape appears, and if it is a NF trial the 3D model of their hand disappears. The participants task is to trace the shape with the tip of their index finger, moving from the start sphere to a black finish sphere at the opposite end of the shape, while keeping as close to the center of the tube as possible. The primary measure of performance is the trial average of the distance between the fingertip and the center of the shape. Figure 3.2 demonstrates a 3D Tracing task trial.

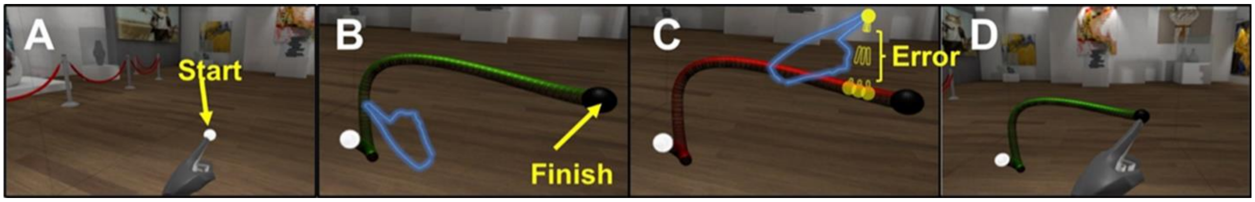

Figure 3.2. 3D Tracing task. A: the participants places the tip of their index finger in the start orb for 2 seconds, which triggers the start of the trial. B: On FF conditions the hand model remains visible, in the NF condition it disappears. The blue outline is used to illustrate the hand during a NF condition, though the participant receives no feedback of the hand. C: performance is determined based on distance from local points at the center of the shape. D: During the FF condition, the participant can see their where they finish. In the NF condition, the participant informs the experimenter when they think they have reached the end. The hand is not made visible until the participant has moved it out the controller field-of-view so as not to provide performance feedback.

Task 2: Reach to Press. In the reach to press task the participant begins the trial with the tip of their index finger in the start sphere. Following a brief delay (a random time between x and y seconds) the start sphere disappears, and if it is a NF trial the 3D model of their hand also disappears. At the same time an icon appears on a virtual touchscreen. Their task is to reach and press the icon with the tip of their index finger. The goal is to press as close to the center of the icon as they can while moving at a natural pace. The primary measure of task performance is the distance between the point on the screen where the participant touched and the center of the icon: a lower score represents better performance. Figure 3.3 demonstrates the reach to press task.

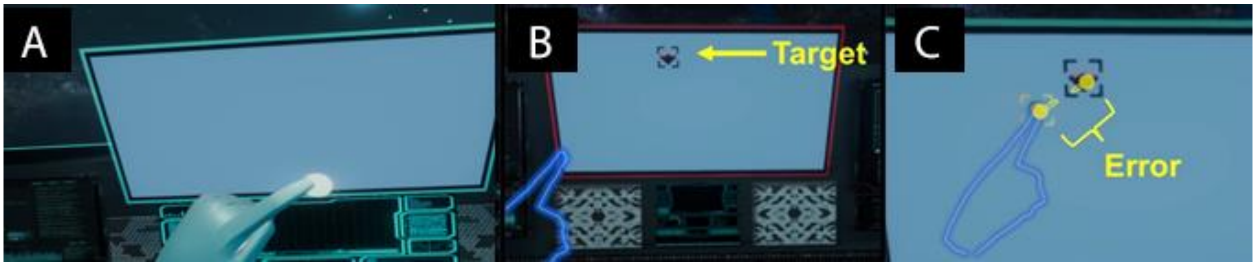

Figure 3.3. The Reach-To-Press task. A: the participant places the tip of their index finger in the start orb for 2 seconds, which triggers the start of the trial. B: a target icon appears on the screen and the participant must reach and press as close to the center as possible. The blue outline illustrates the hand position during a NF condition, though the participant would not see the hand. C: performance error is the distance from the point touched and the center of the icon.

3.1.3 Measures of proprioceptive deficit/capacity

Full Upper-Limb Posture Matching Task (FULPM). The FULPM task uses position trackers fixed to multiple points on each upper-limb to measure the spatial position of limb segments (palm, forearm, and upper-arm; Figure 3.4) while participants assume postures. Unlike most measures of position sense, we do not assess joint angles; instead, we assess the 3D position of limb segments. The FULPM task is performed entirely while seated. A head-mounted virtual-reality system is used to occlude vision of participants own limbs while providing a visual task cue. The visual cue is a 3D model of a humanoid figure positioned directly in front of and facing

Figure 3.4. A subject donning the Vive trackers on the limbs (upper arm and forearm) and chest with Vive controllers in hand.

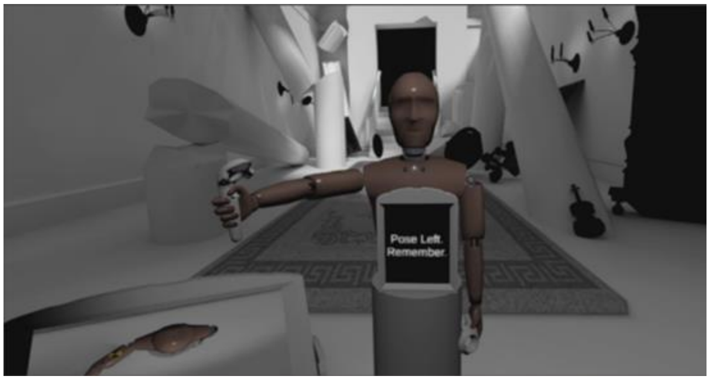

Figure 3.5. The virtual environment seen through the virtual reality headset. The 3D model ("dummy") is presenting a posture for the participant to mirror. On the bottom left of the image is a top down view of the dummy adding an extra point of view for the participant.

towards the participant. The model postures one of its limbs as an example posture and the participant must approximate the posture with their own limb: this posture will be the reference posture (Figure 3.5). Participants are then required to match the posturing of the limb being tested to either the current posture of the contralateral limb (reference limb) or a previous posture of the same limb being tested (reference limb is the test limb). A single score is derived for each trial and represents the average position error between the limb segments of the reference limb and the test limb. Both limbs are tested under all condition. A full description of the FULPM task may be found in Chapter 3 of this dissertation.

Based on results from Chapter 3, the difference between the “affected” limb and the less affected limb (Right error - Left error) from the active memory condition of the FULPM task was used for comparison in this study.

3.1.4 Motor task

The Box and Block test was used as our primary motor assessment. The Box and Block Test is an assessment of manual dexterity and gross arm movement that has been widely used in rehabilitation research as well as clinical settings (Mathiowetz et al., 1985). We chose this task for several reasons, including 1) it is simple to administer and does not take much time, 2) it is a widely used measure used in rehabilitation research including work with stroke patient populations, and 3) it is unlikely to run into floor or ceiling effects.

The standard procedure for the Box and Block Test was followed. A test box with 150 blocks and a partition in the middle was placed lengthwise along the edge of a standard-height table. The patient was seated on a standard height chair facing the box. 150 blocks are placed in the compartment of the test box on the side of the limb that will be tested. When testing began, the patient would grasp one block at a time with the hand, transporting the block over the partition, and releasing it into the opposite compartment. The patient would continue doing this for one minute. The procedure would then be repeated with the nondominant hand. After testing, the experimenter counted the blocks. If a patient transported two or more blocks at the same time, this is noted, and the number subtracted from the total. No penalty was made if the subjects transported any blocks across the partition and the blocks bounced from the box to the floor or table. The task can be seen in Figure 3.6 (Mathiowetz et al., 1985).

Figure 3.6. A participant performing the Box and Block task.

Following the standard protocol described above, the procedure was repeated in a partial visual feedback (PF) condition. All lights in the testing room were turned off and the test was administered in the dark. This condition was always administered following the standard protocol so that participants could become accustomed to the task; this alleviates the concern that had participants started with the PF condition first then their poor performance could be attributable to familiarity with the task as opposed to a difficulty performing when unable to rely on visual feedback of the limb. Thus, we have two feedback conditions: 1) full feedback (FF), and 2) partial feedback (PF).

3.1.5 Study procedure

All testing took place within a single test session in a research laboratory setting. After providing informed consent participants underwent screening to determine whether they qualified to participate. If they qualified and still desired to participate the testing session began. Figure 3.7 depicts the order tests were administered for stroke patient participants. All patients and controls underwent the same testing procedures.

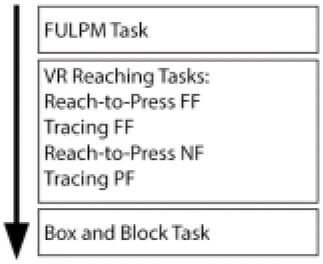

Figure 3.7. Study design.

3.2 Analyses

All data preprocessing and analyses was performed in C# (Microsoft Corporation, 2000-2020) and R (Team, 2016).

Multi-factor significance testing was conducted using linear mixed models (fit using restricted maximum likelihood [REML]). Mixed models were implemented using the ‘lme4’ package for R . Participant “ID” was included as a random effect to account for repeat measurements across limb (left/right) and feedback condition (ff/pf) within subjects. Below is an example model using the lme4 package which tests the main effects of ‘Group’, ‘Feedback Condition’, and ‘Limb Tested’, as well as all possible interaction effects, on our ‘DV’; “ID” is included as a random effect:

$$lmer(DV \sim Group * Feedback * \ LimbUsed + (1|ID), data = \ TestData)$$

Post-hoc testing using Tukey’s method for p-value adjustment was used to interpret significant interactions; post-hoc tests were implemented using the ‘emmeans’ package for R.

Subject mean scores were calculated per control participant per condition. Patient participants were treated as case-studies, therefor all patient data points were included. Welch's two-sample t-tests were used for simple group comparisons; two-sample paired t-tests were used for simple within subject comparisons.

The 'lmer' function we used to build and test linear mixed models utilizes Satterthwaite's method for approximating degrees of freedom (1941) and the 'emmeans' function we used in post-hoc testing utilizes Kenward-Roger approximation (1997). These methods of degrees of freedom approximation, as well as the REML approach to estimating variance, have been shown through simulations to produce acceptable Type 1 error rates, even in small samples (Luke, 2017). However, this is a pilot study which aims to establish the FULPM task as a measure suitable for use in healthy individuals and stroke survivors. Significance tests were conducted to identify potentially significant factors for future study. Caution should be taken in interpreting test results given small sample sizes.

Patient case-studies are handled primarily through data exploration in lieu of significance tests.

3.3 Results

$$lm(TraceError \sim Group * Condition * \ LimbUsed)$$

Tracing performance degradation is significantly greater in patients' affected limb during the NF condition. A simple linear model including only patients found a significant interaction between feedback condition and the limb used [β=1.79, t=3.87, p<0.0001], which included a significant increase in error for the affected limb during the NF condition [β=-1.03, t=-4.4, p=0.0001], see Fig 3.8 for Tracing task results.

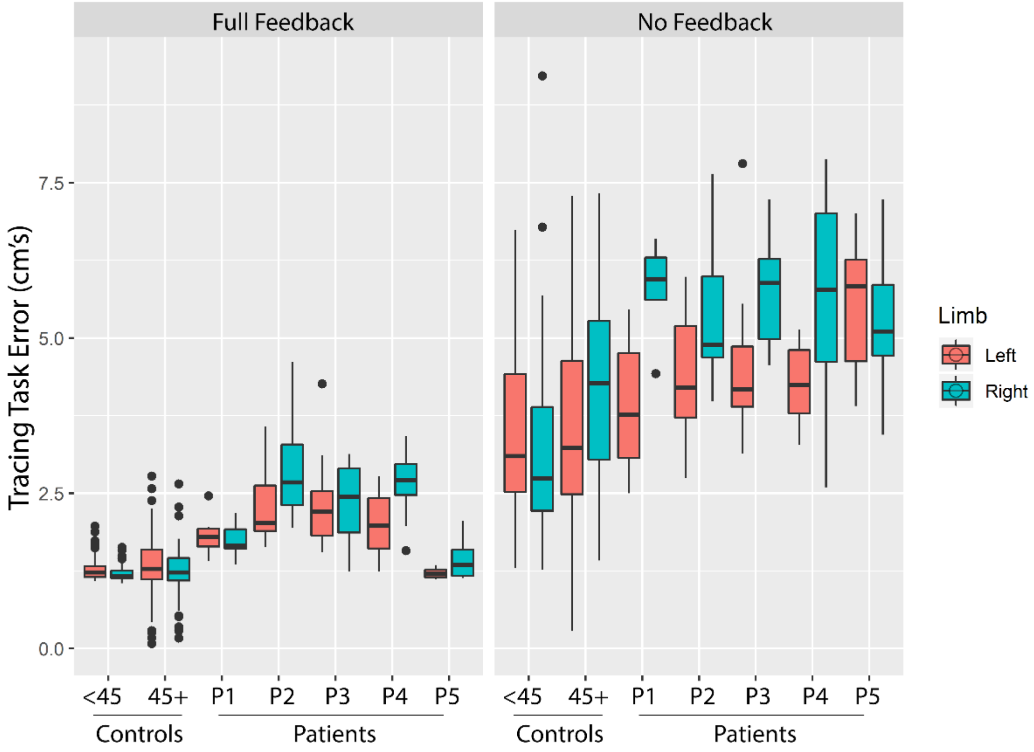

Figure 3.8. Performance on the tracing task across feedback condition and limbs.

$$lmer(ReachtoPressError \sim Group * Condition * \ LimbUsed + (1|ID))$$

Error in the Reach-to-press task is greater for the NF condition, regardless of group. We found a main effect of feedback condition [β=1.79, t=3.87, p<0.0001], with performance being significantly poorer during the NF condition (M=3.2, SD=1.86) compared to the FF condition (M=1, SD=0.48), see Fig 3.9 for tracing task results.

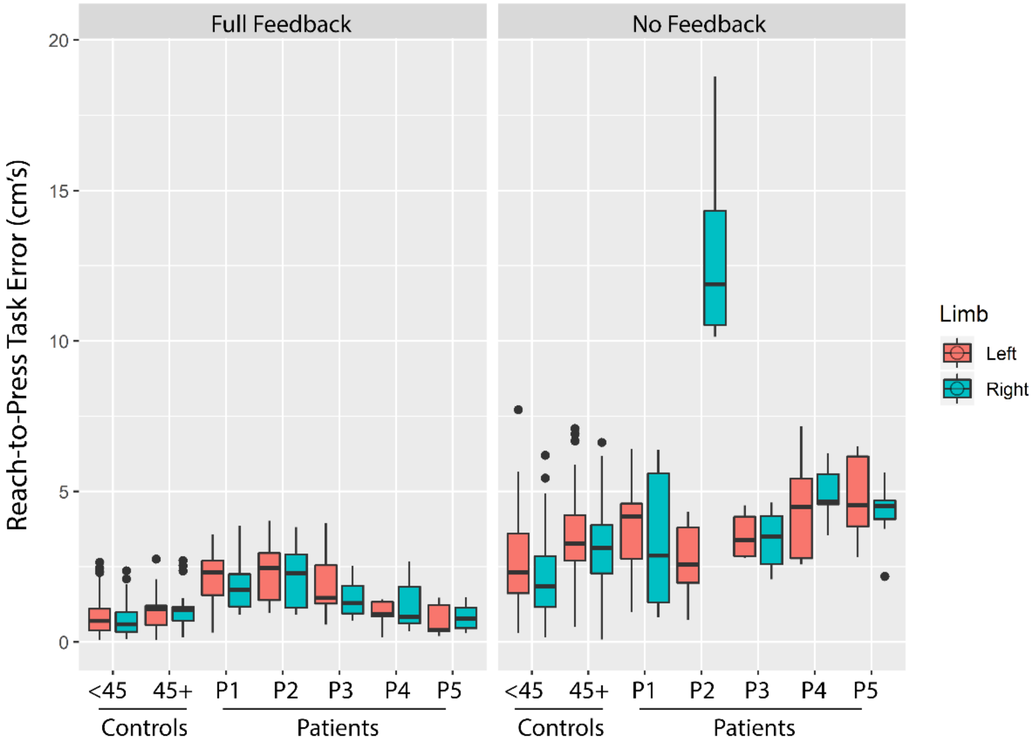

Figure 3.9. Performance on the Reach-to-press task across feedback condition and limbs.

Reach-to-Press performance is not significantly different between feedback conditions among patients. As predicted, patient's performance was not significantly different during the ballistic reaching task.

There may be a relation between tracing and Box and Block performance, and FULPM error when using the affected limb during the NF condition. Based on the existing data (Fig 3.10), it seems plausible that FULPM error (proprioceptive deficit) is associated with sensorimotor performance in the tracing task, though larger samples would be necessary to draw firm conclusions. A similar trend seems plausible in the Box and Block task (Fig 3.11).

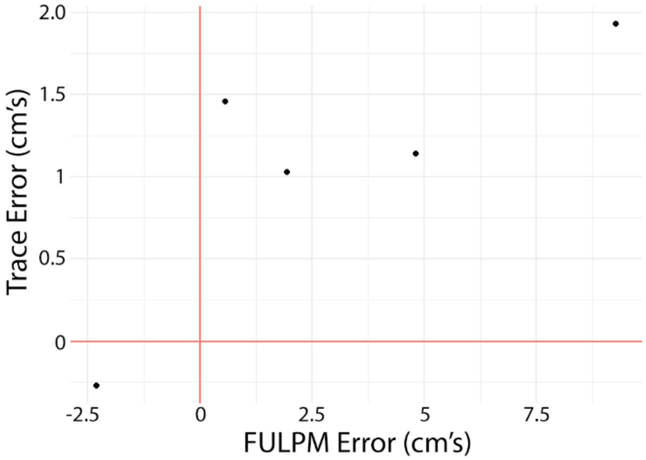

Figure 3.10. Performance on the Box and Block task across feedback conditions.

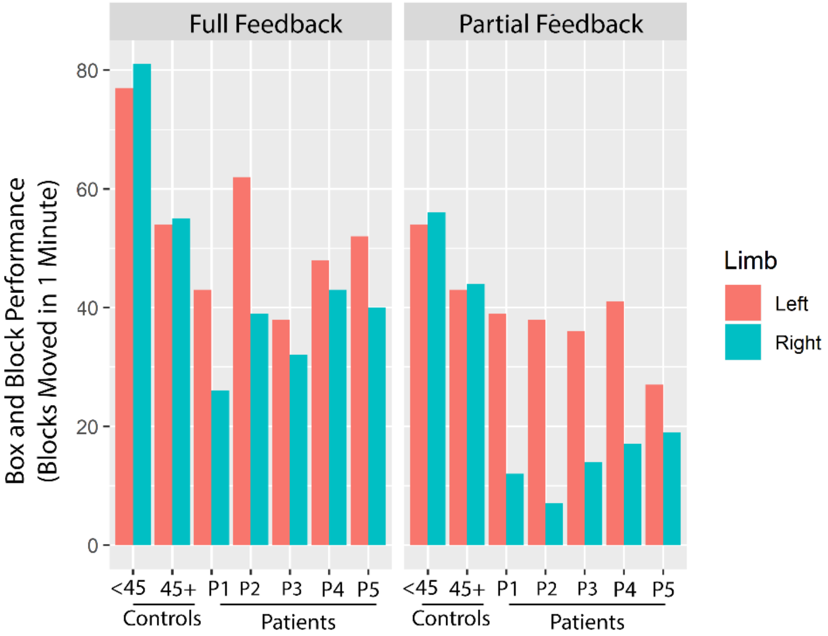

Figure 3.11. Performance on the Box and Block task across feedback conditions.

Among controls, Reach-to-Press and Trace performance is more difficult in the NF condition, though especially for the older control group. Additional comparisons identified differences between control age groups. Error was significantly greater on the NF condition (M=2.7, SD=1.1) compared to the FF condition (M=0.8, SD=0.3)[β=-1, t=-11.2, p<0.0001], regardless of age group. There was a significant interaction between age group and feedback condition [β=0.2, t=2.3, p=0.03], which pairwise comparisons indicate includes a significant decrease in performance for the older group during the pf condition [β=0.2, t=2.3, p=0.03].

Trace task performance was significantly better during the FF condition (M= 1.3, SD=0.3) compared to the NF condition (M=3.4, SD=1)[β=-1.1, t=-14, p<0.0001], regardless of age group. The interaction between age group and feedback condition approached significance [p=0.07].

3.4 Discussion

While we have a basic understanding of proprioception's role in typical motor control and motor learning, less is known about how proprioceptive deficits in stroke survivors affect motor control strategies. As hypothesized, performance degradation is most acute during the NF condition with the impaired limb in the tracing task, which requires controlled movement, rather than simple reaching movements used in the Reach-to-Press task. While our initial assessment of a patients' impaired limb was based on self-report, the active memory condition of the FULPM task corroborated their reports (aside from patient 5) and their proprioceptive deficit appears to be related to the degree of performance degradation on the tracing task as well as the Box and Block task. Patient 5, notably, showed similar performance degradation across both limbs in the NF conditions of the tracing task and the Box and Block task. It is possible that unnoticed bilateral deficits equally impact their performance.

While the next immediate step is to properly validate the FULPM task and its connection with motor performance, there are promising avenues beyond that. Previous studies suggest that proprioceptive training of the upper limb may be possible, via removing online visual feedback of the limb (Byl et al., 2003; Leeanne Carey et al., 2011; LM Carey et al., 1993; Cho et al., 2014; Hughes et al., 2015; S. I. Kim et al., 2013). We may be able to use these tasks to train proprioception and improve proprioceptive capacity. Alternatively, it is possible the tracing task, and other similarly challenging and controlled motor task could be used as a proxy measure of proprioceptive capacity.

This is an important step in identifying the functional implications of proprioceptive deficits in stroke patients. Importantly, we used tasks which require natural reaching as opposed to tasks with poor ecological validity like performance using planar robots. These preliminary results are promising, though recent work in stroke patients using planar robotics has shown that not all patients adapt to proprioceptive deficits in the same way (Semrau et al., 2018). Understanding the mechanisms that uniquely impair our ability to estimate our body state could lead to both a better understanding of proprioception in general as well as more appropriate clinical interventions in the various patients that live with proprioceptive deficits.

Chapter 4: The Neural Correlates of Non-Visually Guided Grasp in Humans

There is an abundance of evidence that parieto-frontal networks play a key role in visually-guided reaching and grasping in human and non-human primates (Begliomini, Caria, et al., 2007; Begliomini et al., 2014; Begliomini, Wall, et al., 2007; Binkofski, Buccino, Posse, et al., 1999; Binkofski, Buccino, Stephan, et al., 1999; Binkofski et al., 1998; Castiello & Begliomini, 2008; Culham et al., 2006, 2003; Frey et al., 2005; S. Grafton et al., 1996; S. T. Grafton et al., 1996; Valyear, n.d.). Studies have predominantly focused on visually guided reach/grasp behaviors and thus the parieto-frontal network has become the de facto "visual-grasping" network. However, there is evidence which suggests that extrinsic (visual) and intrinsic information (proprioceptive, feed-forward prediction) regarding the upper-limb is processed by these networks (M Jeannerod et al., 1995; Murata et al., 1996, 2000; Sakata et al., 1995; Taira et al., 1990). Single-cell recordings in macaque anterior intraparietal area (AIP) has identified cells uniquely tuned to grasping with vision as well as cells that activate equally to or even greater when grasping without vision (M Jeannerod et al., 1995; Sakata et al., 1995; Taira et al., 1990). Visual grasping research has shown that human anterior intraparietal sulcus (aIPS) is functionally similar to monkey AIP in many respects, though there has yet to be evidence of similar visually agnostic activity within human aIPS. Research in human and non-human primates that has required grasping without visual feedback of the limb have also removed vision of the object, leaving open the possible alternative explanation that enhanced activity is related to grasping while relying on memory of the object; this is a plausible explanation given the role of aIPS in hand pre-shaping to object features (Eugene Tunik et al., 2005). Evidence in human neuroimaging also implicates the superior parietal occipital cortex (SPOC) in intrinsic processing of wrist position during grasping (Monaco et al., 2011).

We address this issue by using a factorial design to identify the effects of visual feedback on grasp-specific responses within specific areas of the parieto-frontal grasp network by selectively removing vision of the hand and limb during grasp while retaining vision of the target object. If responses in aIPS and SPOC depend on visual feedback, responses will be diminished when performing in the dark. By contrast, if aIPS and SPOC are involved in the control of grasping independent of visual feedback then we expect comparable grasp-specific responses under conditions with and without visual feedback.

We hypothesize that we will observe activity related to non-visual grasp in these key regions (based on human and monkey research): IPS (Murata et al., 2000; Sakata et al., 1995; Taira et al., 1990), SPOC (Breveglieri et al., 2016; P Fattori et al., 2010; Patrizia Fattori et al., 2004; Patrizia Fattori, Breveglieri, Bosco, Gamberini, & Galletti, 2017), IFG (S. T. Grafton et al., 1996), SMA (S. T. Grafton et al., 1996; Mason, Theverapperuma, Hendrix, & Ebner, 2004) and the premotor cortices (BA6; including vPMC and dPMC) (S. Grafton et al., 1996; Murata et al., 1997; Raos et al., 2006; Rizzolatti et al., 1988).

4.1 Methods

4.1.1 Subjects

22 healthy participants were recruited to participate in this study. Two participants were excluded due to techincal errors with the MRI equipment. The results are based on the reamining 20 subjects.

All patient and control participants gave informed consent in accordance with local ethics committee recommendations.

4.1.2 Presentation apparatus

We designed an MR-safe object presentation apparatus which allowed for 16 uniquely shaped grasp targets to be presented to participants at approximately 10cm above the waist. The apparatus utilized a slide mechanism for interchanging objects between trials while the participant was within the MRI scanner bore. Participants viewed the object workspace, consisting of the participants' arm/hand and the apparatus/object, through a double mirror attached to the Siemens head coil. Four fiber optic fiber cables were routed to the apparatus from an enclosure containing an Arduino Leonardo with related super-bright colored LED electronics, located on the other side of the patch panel inside the MR control room. The colored optic fibers, when lit, were used to manipulate object and workspace visibility (white), as well as provide a Fixation light (yellow) and instruction cue lights (blue and red), See Figure 4.1.

4.1.3 Grasp/Touch targets

We created 16 uniquely shaped target objects based on previous work by Blake et al. in (Blake & Brady, 1992) robotics research. The shapes were designed to provide limited optimal points of contact when using a pincer-grasp. We chose to use these shapes to provide a challenge to participants, requiring them on each trial to select optimal grasp points. An example object can be seen in Figure 4.1.

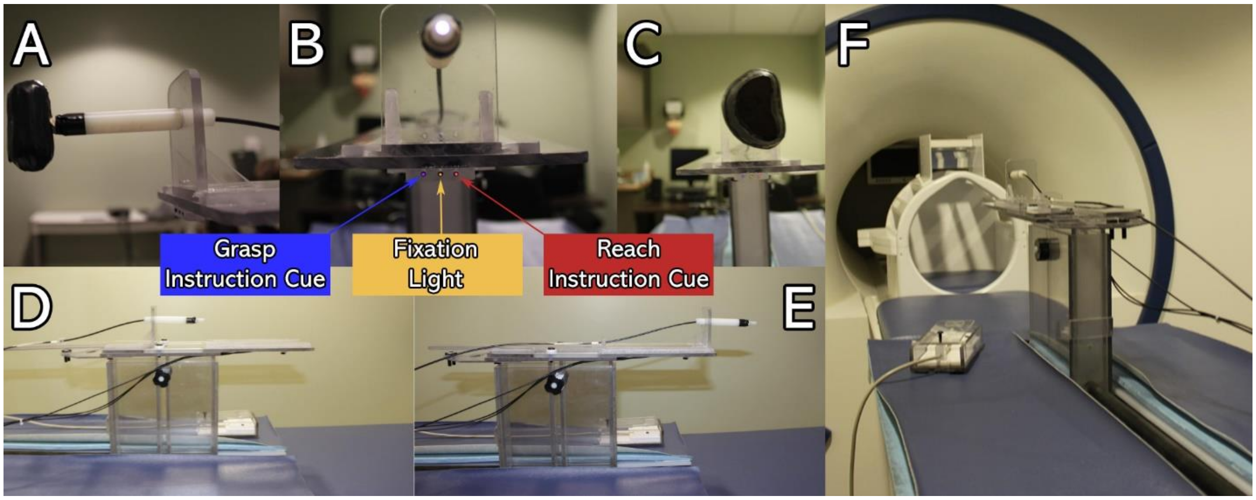

Figure 4.1. Object presentation apparatus. A: Target object attached to illumination fiber mounting post. B: Front view of the presentation apparatus without an attached object. Directly beneath the illumination fiber mounting post is the fixation light and the two instruction cue lights. C: Front view of the presentation apparatus with an attached object, as seen from the participants point-of-view. D: The illumination fiber mounting post is attached to a slide mechanism used by the experimenter to exchange objects between trials. Here the slide is retracted (to swap objects). E: The slide is fully extended (for participant interaction). F: The presentation apparatus on the mock scanner bed (similar configuration to the fMRI scanner). Affixed to the top of the coil is a mirror which allows participants to see the workspace. Once a participant is situated on the scanner bed with their head in the coil, the presentation apparatus can be adjusted so that the mounted objects are within arm's reach, and at a comfortable height and distance from the participant's waist, which helps prevent bodily motion.

4.1.4 Scanner bore illumination

Two 10mm diameter optical fibers were attached to the bore wall above the participant, at 45- and 135-degree points in the bore circumference, which transferred light from super-bright white LEDs housed within an enclosure in the MR control room. The LEDs on/off state were controlled through the Arduino Leonoard that was connected to the parallel port of the stimulus presentation computer. The scanner bore lighting allowed the particpants vision of the entire workspace and their limb to be controlled selectively.

4.1.5 Response box

Response and movement times were recorded using an MR safe response button. While at rest, the participants right hand rested on the button, which by default was positioned at waist level. Once participants finished the grasp/touch movement action, they promptly returned to the button. Reaction time was determined as the time the participant lifted their hand from the button box relative to the onset of the object illumination. Movement time was defined as the total time between button lift and return of the hand to the button.

4.1.6 Mock scanner and training

The participant was trained to perform the task, ahead of the experiment, in the mock scanner. The training session was conducted in order to acclimate the participant to the scanner environment and to ensure that the participants understood the task. LED lights were used to provide workspace lighting in the mock scanner. See Figure 4.1.

During the training session, the experimenter was discreetly given auditory cues indicating which action the participant should be performing for the next trial. Participants were immediately corrected if the incorrect action was performed or if the correct action was performed improperly. Each participant performed 16 trials of the task during the training session.

4.1.6 MR procedure

Participants were situated on the gantry with the presentation apparatus adjusted so that objects were reachable with minimal effort or extraneous movement. A strap was used to secure the upper arms, preventing shoulder movement, and foam was used to pad around the head, both efforts to prevent movement of the head. The response box rested on the participants’ right thigh to avoid shifting once a trial had begun. Once the participant was fully positioned within the scanner, with right hand rested on the response box, all lights were turned off. From within the scanner room, all sources of external light were blocked.

On each trial, participants were to maintain their gaze on a fixation light when not engaging in an action. At the beginning of a trial the entire workspace was dark except for the fixation light. The onset of a cue light (red or blue) determined which task to perform: reach to grasp or reach to touch. After a short delay, the object was illuminated. On half of the trials, object illumination was paired with illumination of the entire workspace, via the bore lights. The participant was instructed to initiate the instructed action upon illumination of the object. Once the touch/grasp had been performed participants returned their hand to the default position on the response box. Shortly after an action had been completed, a discrete tone cued an experimenter within the scanner room to change out the object. See Figures 4.2 and 4.3.

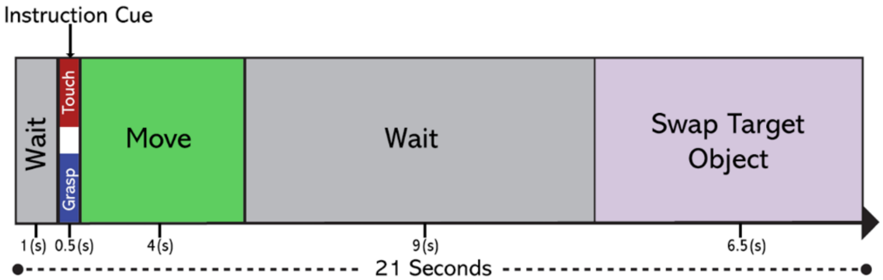

Figure 4.2. Sequence of events for a single trial.

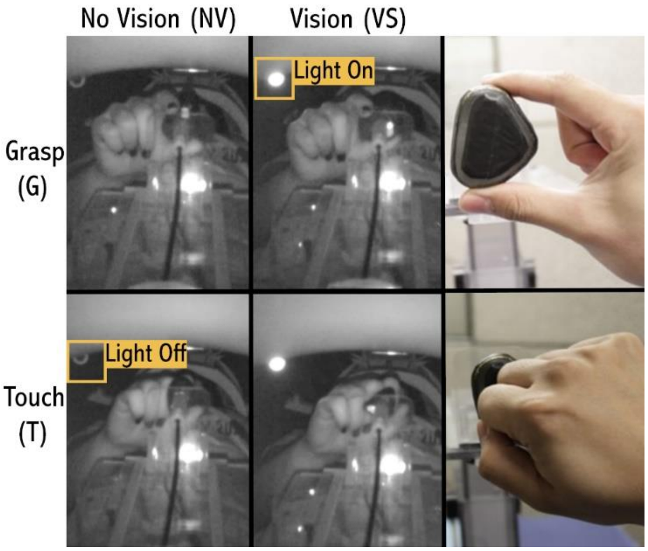

Figure 4.3. 2 x 2 Experimental Design Conditions. G = “Grasp,” T = “Touch,” NV = “No visual feedback,” VS = “with visual feedback”. The far-right images show the correct pincer grasp or closed fist touch, as demonstrated to participants during task training.

When a run was complete (16 trials), the main lights within the scan room were turned on, which prevented the participant from adapting to the low light conditions. During this time the experimenter reorganized the 16 objects in the correct order for the next run. See Figure 4.2.

4.1.7 Imaging parameters

Imaging was performed on a 3-Tesla Siemens TIM Trio MRI scanner with a conventional 8-channel birdcage head coil. The T1-weighted anatomical images were collected using a multiplanar rapidly acquired gradient echo (MP-RAGE) pulse sequence: time to repetition (TR) = 1920 ms; time to echo (TE) = 2.92 ms; flip angle = 9; matrix size = 256 x 256; field of view (FOV) = 256mm; 176 contiguous sagittal slices; slice thickness = 1mm; in-plane resolution = 1 mm x1 mm. Auto Align Scout and True FISP sequences were executed before the start of each functional run to ensure that slices were prescribed in exactly the same positions across runs. Functional MRI volumes were collected using a T2*-weighted single-shot gradient-echo echo-planar imaging (EPI) acquisition sequence: TR = 3000ms; TE = 30ms; flip angle = 84; matrix size = 64 x 64; FOV = 200 mm; slice thickness = 3 mm; in-plane resolution = 3.125 mm x 3.125 mm; acceleration factor (integrated parallel acquisition technologies, iPAT) = 2 with generalized auto calibrating partially parallel acquisitions (GRAPPA) reconstruction**.** Lastly, a gradient echo field map scan was acquired for distortion correction of the EPI images.

4.2 Data preprocessing and analysis

Structural and functional fMRI data was preprocessed and analyzed using fMRIB's Software Library [FSL v.5.0.8 (http://www.fmrib.ox.ac.uk/fsl/)] (S. M. Smith et al., 2004). Each functional run was assessed for subject head motion using motion-detection parameter plots generated by FSL 3-D motion correction algorithms on the untransformed two-dimensional data. Non-brain structures were removed using BET. Functional data were preprocessed with high-pass temporal frequency filtering to remove frequencies below 0.01 Hz. Functional volumes were then aligned to high-resolution anatomical volumes using FLIRT, and transformed to standard stereotaxic space (Montreal Neurological Institute, MNI-152 template) using FNIRT nonlinear registration algorithims. Data were spatially smoothed using a Gaussian kernel of 6 mm (full-width at half-maximum).

Data were analyzed at single-subject levels using fixed-effects general linear models (GLMs), carried out in FEAT v.6.0, with FILM applied to correct for serial correlations (S. M. Smith et al., 2004). To enable valid between-run and -subject statistics, each run underwent intensity normalization using “grand mean scaling”, effectively giving each run a mean signal of zero and converting beta weights to units of standard deviations. Group-level voxel-wise analyses were implemented using random-effects, FLAME 1.

GLMs included independent explanatory variables (EVs) per condition, and their temporal derivatives. Condition-specific EVs were modeled as rectangular wave functions, high during the condition and low during all other conditions, convolved with a double-gamma basis function to estimate spatiotemporal properties of the BOLD response, aligned to action onset cues (object/workspace illumination). For runs without Errors, “dummy” predictors comprising columns of all zeros in the design matrix were included. Additional EVs of non-interest included head motion translation/rotation parameters from motion correction outputs, and spike predictors corresponding to abrupt signal changes between temporally adjacent volumes of ±1SD from the mean, as identified using FSL outlier detection.

A total of 2,688 trials were collected (672 per condition) from 20 participants. For all four conditions, the period of interest was defined as the four second period during which the target objects were illuminated. The remaining time was treated as an implicit rest period.

The contrasts G-VS > rest, G-NV > rest, T-VS > rest, and T-NV > rest were used to identify voxels significantly activated by the task. As expected, this revealed widespread activation of sensorimotor areas, including bilateral primary motor and somatosensory, secondary somatosensory, dorsal and ventral premotor, posterior parietal and cingulate motor areas, as well as the thalamus, basal ganglia, and cerebellum. These contrasts were combined to create a functional inclusion mask to constrain subsequent contrasts. The purpose of this method was to increase the sensitivity of subsequent statistical tests by reducing the number of voxels considered for correction for multiple comparisons to those that showed task-related activity increases.

Region of interest analyses were performed to investigate the vision-selectivity of areas of significant activation identified in our whole-brain voxel-wise analyses. We have included the results from two ROI analysis approaches, as well as the merits and justifications for each. In each approach we are testing the hypothesis that the difference in percentage BOLD signal change for (G-NV) - (T-NV) will be significantly greater than for (G-VS) - (T-VS). We tested these hypotheses using one-tailed paired t-tests and have defined significance as a p-value less than or equal to $p = 0.05$. Both approaches make use of anatomical masks created from structural atlases. These masks indicate a subset of voxels likely to represent each region of interest. ROI's for aIPS and the SPOC were defined using the Juelich histological (cyto- and myelo-architectonic) atlas references; all remaining ROI's were defined using the Harvard-Oxford cortical structural atlas. Structures were defined unilaterally at a minimum subject-overlap threshold of >30%, except for SMA, which was defined bilaterally.

Our first ROI analysis probes the direction of effects within anatomical ROI's while restraining our query to significant voxels from the whole-brain voxel-wise interaction: (G-NV>T-NV)>(G-VS>T-VS). We created ROI masks by intersecting the group-level interaction results with each anatomical ROI: per anatomical ROI, only the voxels from the interaction map with a z value of

2.0 or greater (p = 0.02) were retained. The resultant voxel masks were used to assess percentage BOLD signal change per subject for each condition contrasted against rest (GV > Rest, GNV > Rest, RV > Rest, RNV > Rest). This approach is a necessary complement to the whole-brain voxel-wise analysis, though because we are constraining the analysis to voxels from the interaction contrast we are unable to form conclusions about the predominant visual-selectivity within each region of interest, if there is any.

Our second ROI analysis approach explores whether subject specific peak activation related to grasping, regardless of visual feedback, showed significant visual selectivity (i.e., greater activation with or without visual feedback). We created subject specific ROI masks by first intersecting each subjects' main-effect of grasp contrast (Grasp > Reach) with our anatomical ROI's (as described earlier), creating functional ROI maps. We identified the voxel with peak activation for each resultant functional ROI map. For each subjects' peak voxels we created a binarized sphere mask (10mm diameter) centered on the peak voxels coordinates. Concurrently, binarized masks were created for each subjects' main-effect of Grasp contrast (Grasp > Reach) using a threshold of z = 2.0 (p = 0.02). Each subjects' sphere masks were intersected with the voxels from their binarized main-effect of grasp mask. The resultant voxel masks were used to confine the ROI analyses for the main effect of each condition over rest (GV > Rest, GNV > Rest, RV > Rest, RNV > Rest).

4.3 Results

4.3.1 Whole-Brain voxel-wise analyses

In the following voxel-wise contrasts we subtracted grasp trials from touch trials in order to isolate the action of grasping and remove activity related to reaching or making contact with the grasp object in a non-grasping context.

Subsets of the grasp network show stronger activation when grasping without visual feedback. To assess the effect of visual feedback during grasping, we analyzed the following interaction: (G-NV>T-NV)>(G-VS>T-VS). The interaction revealed significant activation in IPS and the superior parieto-occipital cortex (SPOC; i.e., medial extent of Brodmann area 7), as well as the supplementary motor area (SMA), the IFG (BA44/BA 45), and the premotor cortex (BA6), as shown in Figure 4.4A and 4.4B.

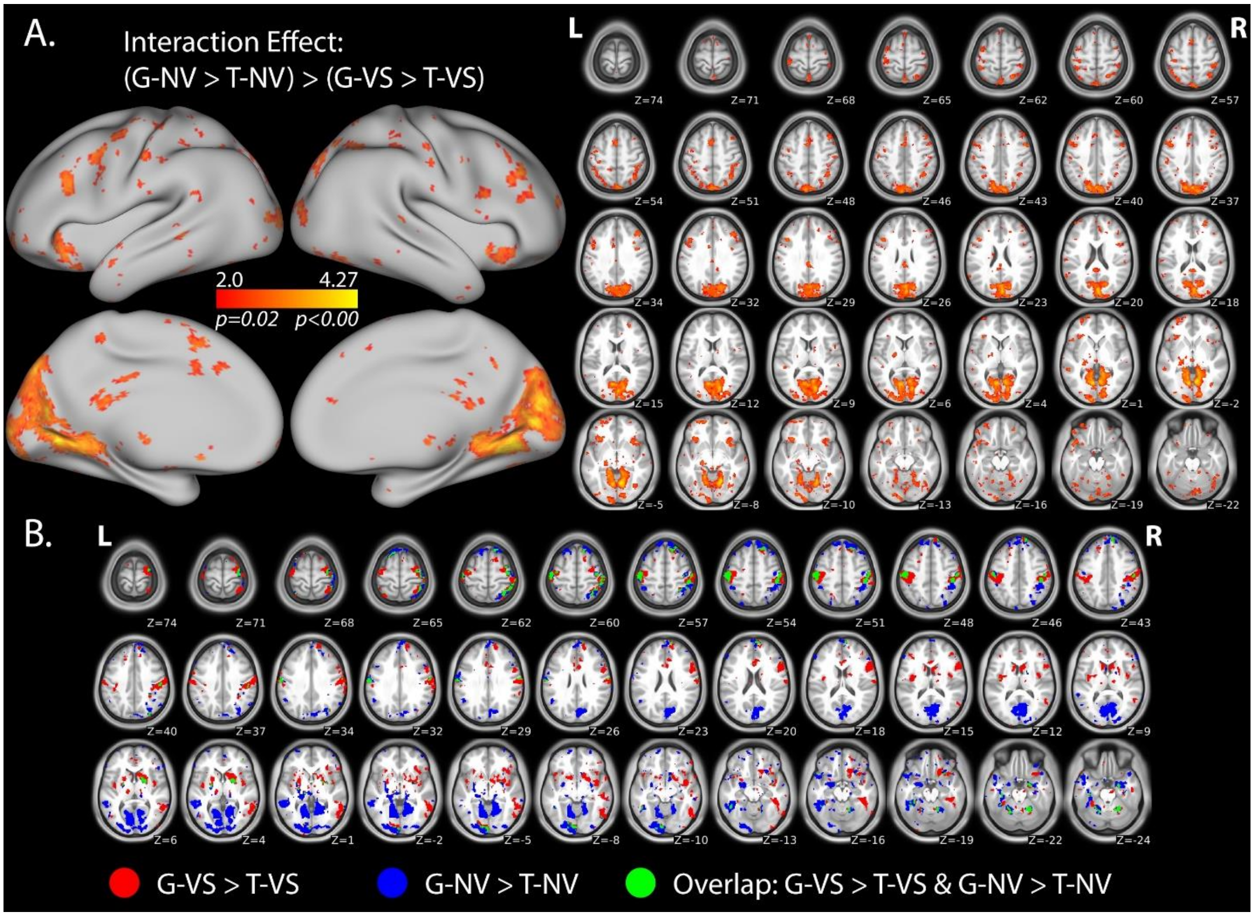

Figure 4.4. Whole-Brain Voxel-Wise Results: Interpreting the Interaction. A: Surface (Left) and Volume (Right) activation for the interaction effect, which aims to isolate non-visually guided grasp activity. B: Binarized maps of the simple main effects of grasp as well as their intersection (green).

Grasping reliably activates the anticipated fronto-parietal grasp network. We analyzed the contrast of grasp over touch (Grasp > Touch), ignoring the condition of visual feedback. Our results replicated prior studies, showing predicted activation of the parieto-premotor grasping network, including activation in all hypothesized regions of interest, as shown in Figure 4.5.

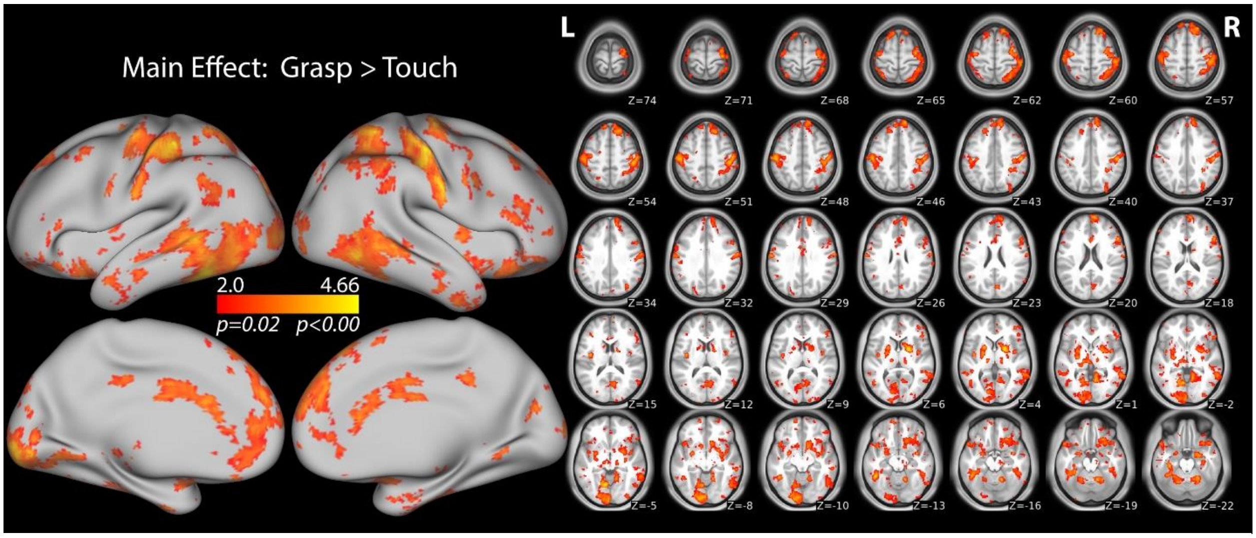

Figure 4.5. Whole-Brain Voxel-Wise Results: Main Effect of Grasping. Surface (Left) and Volume (Right) maps for the main effect of grasping, regardless of visual condition. We see activation within anticipated regions of the fronto-parietal grasp network.

The whole brain voxel-wise results suggest that subsections of the fronto-parietal grasp network may be involved in grasping without visual feedback of the limb (this can be seen in the overlapping contrasts in Figure 4.4A/B). For each of our hypothesized regions we found significant activity, though given the nature of the interaction contrast, further tests were needed to identify whether significant activation is specific to grasping without vision. Figure 4.4B shows the overlap between the contrasts G-VS > T-VS and G-NV > T-NV, which gives an idea of which voxels from our main effect of grasp contrast (G > T) may show specificity for grasping without vision. To interpret our primary contrast of interest, the interaction contrast: (G-NV>T-NV)>(G-VS>T-VS), we performed a series of region of interest (ROI) analyses.

4.3.2 Region-of-Interest analyses

To investigate the visual selectivity of areas well-known to be involved in visual reach-to-grasp, we queried our hypothesized regions of interest, which were all implicated in our whole-brain voxel-wise analyses. We analyzed the following regions: left and right IPS, left and right SPOC (the medial extent of Brodmann area 7), the supplementary motor area (SMA), left and right inferior frontal gyrus (IFG; including BA44 and BA45), and left and right premotor cortex (BA6, excluding SMA).

ROI approach 1: Increased BOLD signal change in the interaction contrast reflects grasping without visual feedback across all ROI's. For all

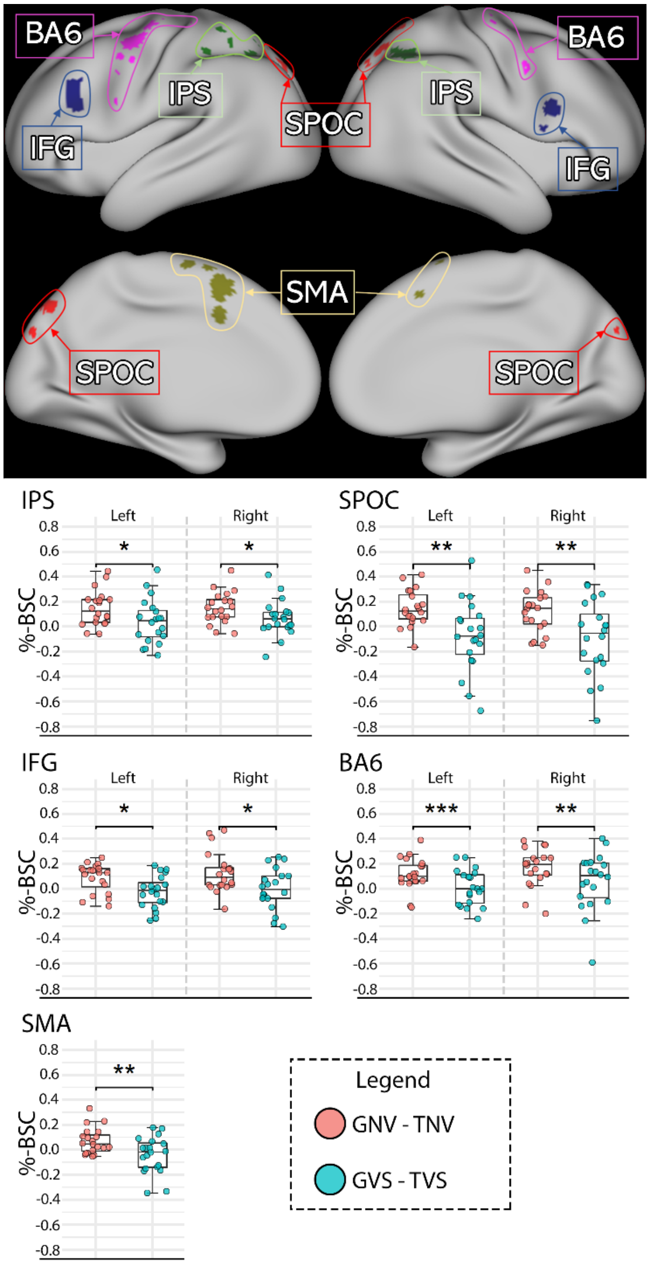

Figure 4.6. Results of ROI approach 1. Top: active voxels (z>=2.0) from the interaction contrast constrained by each anatomical ROI. All hypothesized ROI's show the same visual-feedback selectivity: significantly greater percentage BOLD signal change (%-BSC) when grasping without visual feedback.

ROI's we found significant effects ($p < 0.05$) in favor of our hypotheses. Results for each ROI can be seen in Figure 4.6.

ROI approach 2: Voxels surrounding the peak activation within all ROI's were not visually selective. We found no significant difference in percentage BOLD signal change based on visual feedback condition across any ROI's. Two regions were bordering on significant, with a trend of greater BOLD signal change when grasping without visual feedback: left IPS (P = 0.056) and left BA6 (P = 0.058). The distribution of peak activation across all subjects (per ROI) can be seen in Figure 4.7.

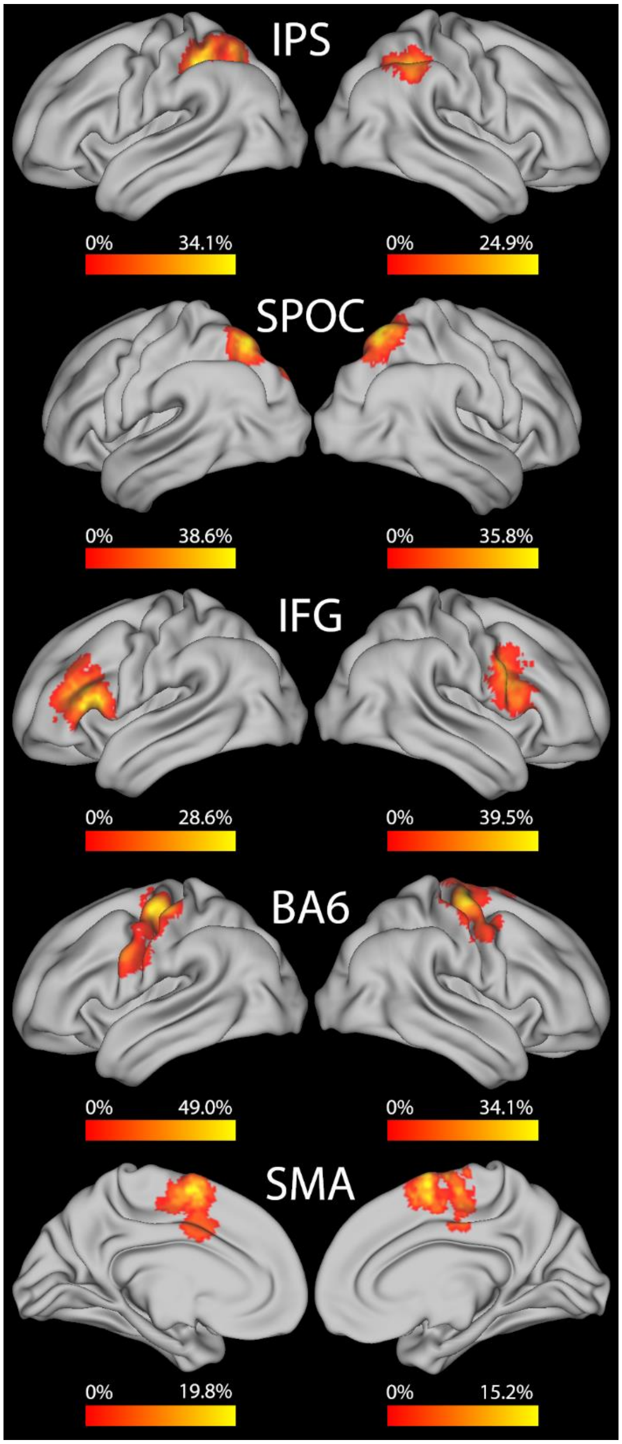

Figure 4.7. Heat-map's showing the percentage overlap of predominate significant ($z>=2.0$) grasp (Grasp > Reach) activity across all participants from ROI approach 2.

4.4 Discussion

Past human and non-human primate grasping research has robustly identified a parieto-frontal grasp network, or grasp circuit, which includes substantial regions of the posterior parietal and premotor cortices, with evidence for distinct functional roles within. This research has primarily focused on visually guided grasping, despite evidence that these regions process both extrinsic (visual) and intrinsic information (proprioception and feed-forward grasping control). We provide the first evidence in humans using functional magnetic resonance imaging that the fronto-parietal grasp network, and key regions involved, are not only extrinsically oriented, but exhibit intrinsically oriented grasp-specific activity. We also provide evidence that predominant activation in these key regions of the grasp circuit are agnostic to visual feedback.

Our whole-brain voxel-wise analyses, further verified using a region-of-interest analysis, identified a subset of voxels from all hypothesized regions belonging to the fronto-parietal grasp network that showed significantly greater activation when grasping without visual feedback of the limb. Our hypothesized regions include the left and right IPS, left and right SPOC (the medial extent of Brodman area 7), the supplementary motor area (SMA), left and right inferior frontal gyrus (IFG; including BA44 and BA45), and left and right premotor cortex (BA6, excluding SMA).

An additional region-of-interest analysis, which queried regions of peak activity within each region-of-interest, and allowed for subject-specific differences in activation, showed that the predominant grasp-specific activity within each region is agnostic to visual feedback (i.e., these regions do not activate more greatly when grasping with or without visual feedback of the hand). This may reflect the networks predominant role in incorporating both extrinsic and intrinsic information relevant to grasp. Though, it is important to note that in this analysis two regions-of-interest, the left IPS and left BA6, were bordering on significance, with a trend of greater BOLD signal change when grasping without visual feedback. A future study with increased power may find prominent roles in processing intrinsic information within IPS and BA6.

Evidence from neuroimaging studies in humans has also implicated the inferior parietal lobule (IPL) in processing proprioceptive information (Ben-Shabat et al., 2015). Later reanalysis including IPL, as well as separating BA6 into the dorsal and ventral premotor cortices, may provide a more thorough understanding on non-visually guided grasp.

These findings corroborate the observation that processing of proprioceptive information is distributed throughout many regions of the brain, without a neural focus (Tuthill & Azim, 2018). It is possible that injury to any one of these regions could result in impaired proprioception important in grasp execution. However, the trend of increased activation in contralateral IPS and BA6 in the NV condition may suggest that these regions are especially important in the non-visual control of grasp. This would make sense given the direct connections between IPS and BA6 and their key importance in multisensory integration for grasp planning and control.

While a larger sample may show a significantly greater role of IPS and BA6 in non-visual control of grasp, an alternative would be to test the causal role of the implicated regions in grasping under different sensory feedback conditions using TMS. This approach could possibly reveal the relative importance of each region, such as whether IPS and BA6 are especially important, as well as show when disruption to each region impairs grasping (e.g., when during the grasp and under which feedback conditions). This will be crucial if we hope to connect this work in healthy adults to neuroimaging in stroke survivors to better predict functional outcomes following neural injury.

Chapter 5: Conclusions

Proprioception is a prime research candidate for rehabilitation focused scientists. Proprioceptive deficits are linked to declines in clinically relevant outcomes and may be a major limiting factor in stroke patient sensorimotor recovery. Despite the considerable role proprioception may play in upper limb motor control and recovery, it is given little attention in rehabilitation practice. As I have interacted with clinicians throughout the course of these studies, it has become obvious that they remain cognizant of proprioceptive deficit and its potential impact on their patients, though they currently have few “tools” to specifically address it. The accepted clinical approach when treating stroke survivors with upper-limb proprioceptive deficit is to encourage reliance on visual feedback, which I strongly suspect limits recovery outcomes; as discussed in Chapter 1, greater proprioceptive capacity in healthy adults is associated with improved motor learning (Fleishman & Rich, 1963) and worse proprioceptive deficit in patients is associated with poorer motor learning (Vidoni & Boyd, 2009), not to mention the observed and theoretical limitations of motor control via visual feedback versus somatosensory feedback (R. L. Sainburg et al., 1995; R. Sainburg et al., 1993; Sarlegna & Sainburg, 2009; Scott, 2016). These observations were a leading motivation in the development of the studies presented in this dissertation. I began with numerous questions and am concluding with many, many more.

This dissertation comprises the first steps in a planned body of research with numerous primary aims, each addressing large gaps in our understanding of somatosensation, the brain, behavior, and recovery. These aims include: 1) identifying more effective rehabilitation approaches for dealing with proprioceptive deficit, 2) developing measures which capture the features of proprioceptive deficit that impact clinically meaningful outcomes (and identifying those features), 3) establishing a better understanding of how/when neural injuries manifest as proprioceptive deficit, 4) discerning the overlap and disparity between proprioceptive modalities (e.g., movement sense versus position sense versus weight discrimination), and 5) relating what we discover in our lab-based assessments of proprioceptive deficit and its effect on performance to “real-world” outcomes. In this final chapter, rather than summarizing each study in sequence, I start by discussing each of these primary aims, including how the studies in this dissertation relate. Most major implications of the studies are encompassed in the discussion of these aims, though section 5.1 is followed by a discussion of the lessons learned from development to exploring study results. While each study presented in this dissertation falls cleanly under one of these aims, my intention is to demonstrate how each study is a precursor to future work that will bring together somatosensation, the brain, behavior, and recovery to advance both our basic understanding as well as rehabilitation practice.

5.1 Long-term research aims

5.1.1 Identifying more effective rehabilitation approaches for dealing with proprioceptive deficit

This aim is addressed first because it was one of my first questions. In fact, the VR reaching tasks introduced in Chapter 3 were originally conceived of as sensorimotor learning paradigms in which alternative feedback (such as visual feedback post-trial or online auditory feedback) is provided so that patients can, possibly, learn to perform when vision of the limb isn’t available. The big question was whether this type of improvement translated to improvement on a distinct measure of proprioceptive deficit, and/or whether those improvements translated to real-world changes in performance. Yet, there were basic questions which needed to be addressed prior to a study of that nature. Some of those questions were the seeds of this dissertation.

For one, we have seen in past research that complete proprioceptive loss due to large fiber neuropathy results in major motor impairment and a strong reliance on visual feedback of the body. Yet, it was unclear whether the same was true for stroke patients, who show impairments, though not a complete loss of somatosensation. As my studies were underway, evidence arose in the literature that corroborated my hypotheses that (at least some) stroke survivors with proprioceptive deficit rely on visual feedback/monitoring and that visual feedback isn’t an ideal compensatory strategy (Semrau et al., 2018). The study reported results from an impressively large sample size amongst the stroke sensorimotor literature (N=281). In this study, nearly 40% of individuals with proprioceptive deficits were able to return to typical performance with visual feedback. Of those that couldn’t compensate with visual feedback, 57% exhibited visual neglect and/or visual field deficits. The remaining 43% without visual deficits still showed significant deficit with vision. The task used in the study required online corrections, albeit movements were made using a planar robot on a 2-dimensional plane. In all, the task was more apt than most used in the reach to grasp literature, though was still a long shot from realistic activity. What remained unclear was how these ratios might change were the task more/less demanding of sensory feedback.

The study by Semrau et al. was asking slightly different questions than my own. The task itself required participants to match passive movement of their unaffected limb (moved by the robot) with active movement of their affected limb; my study was comparing independent performance of each limb across two tasks with unique demands: the reach-to-press task was similar to traditional simple reaching tasks, whereas the tracing task demanded feedback-controlled movement. Their study posited their questions in terms of performance improvements with vision, as opposed to performance reduction without vision. This brings up an important point: as opposed to a general linear relationship between proprioceptive deficit and performance under varied feedback conditions, patterns of performance across feedback conditions may vary based on a number of factors, such as sub-acute visual deficits or difficulties with multi-sensory integration (a very likely concern with injury to the posterior parietal cortex). It is possible that eventually we will be able to predict what changes in performance we will see based on the types and severities of comorbidities, though in practice we are still a long way off. In Chapter 3, we tested the hypothesis that stroke survivors with proprioceptive deficits do rely on visual feedback, though most prominently when the task is challenging and can't be accomplished through feedforward/ballistic movements. Despite a limited sample, we found that, as hypothesized, performance degradation in the affected limb was significant when visual feedback was removed, and when the task required controlled movements. While significant at a group level (and looking at raw data, which violates assumptions of independence), the individual results weren't so straightforward. What we found was that 1 of 5 participants performed significantly worse with their affected limb when vision of the limb was absent, across both tasks. We found that 3/5 participants performed worse with their affected limb without vision only on the tracing (more demanding) task. The last participant showed a decrease in performance without visual feedback, though the decline in performance was similar between limbs. This could be a sign that the participant does not suffer from significant proprioceptive deficit, that their deficit is qualitatively different, that their injury was bilateral (my leading hypothesis), and/or they are dealing with other major comorbidities (such as weakness). Patient 5 was able to perform the VR tasks without sign of fatigue or discernable issues with limb transport. A planned next step is to perform lesion analysis for these participants, which will confirm whether patient 5's stroke affected both hemispheres of the brain.

Based on my preliminary data from Chapter 3, I think it is reasonable to suspect that the ratios observed in the Semrau et al. study would differ based on task difficulty. This was to be expected based on prior research; depending on the specifics of a task, even sensory neuropathy patients can accomplish 2-dimensional reaching without visual feedback—albeit with diminished quality of movement (R. Sainburg & Ghilardi, 1995; R. Sainburg et al., 1993).

Through my previous research into human reach and grasp, I had formed the opinion that the dynamic ways in which vision and proprioception are utilized in motor control aren't properly appreciated/reflected in most study designs; with further research I may be able to make more concrete claims. A body of research where simple reach and reach-to-grasp tasks are the standard has led to the conclusion that vision of the limb is not important during reach/grasp. However, studies have also concluded that proprioception *isn't* very important in motor control because visual compensation hadn't resulted in significant declines in performance—that is, not on simple reaching tasks (in young healthy college undergraduates). *The task is important.*

A task with relatively low demands, one that *everyone* is highly skilled at because they practice it day in and day out, is not a satisfactory reflection of clinically relevant activity. The existing literature largely ignores the steps necessary to get to that point of expert execution, when online feedback is of lesser concern by nature of familiarity. The sort of actions that are of utmost importance to functional independence are complicated; so are many tasks/hobbies that aren't instrumental to caring for one's self but are none-the-less valued. For example, there is a large disconnect between reaching to grasp a 1-inch square cube that has no functional relevance aside from being grasped in an experiment and knitting or playing the piano. Even planting tulip bulbs in the garden is significantly more intricate than most research paradigms. These examples involve *inter*actions, they require planning and fine motor control based on proprioceptive, tactile, and visual feedback. Typing, writing, and drawing are tasks that most individuals may have decent familiarity with, yet what about the implications for someone who was an “expert”, but following neurological injury has to relearn everything, often in the face of acute changes to their bodily function? I am alluding to proprioceptive deficit, but the same applies to any post-stroke changes.

Depending on my results as I continue to test the link between proprioceptive deficit and performance, adapting my VR tasks or developing similar variants for proprioceptive retraining is a likely next step. Virtual reality offers an affordable and robust addition to rehabilitation. I would argue that it is the best solution to altering feedback conditions while allowing for naturalistic action (i.e., no restrictions to the dimensions of movement and rotation and minimal restrictions to performing in general). Unrestricted movement may be a key feature. As mentioned in Chapter 1, the location of proprioceptive training and pre/post-training proprioceptive assessment matters (at least on a task using a planar robot), meaning unrestricted movement may be necessary for improvements to translate to real world action. Developing such a training paradigm will require further experiments to assess the ideal form of feedback, when it is best to provide that feedback, and whether visual feedback of the hand (i.e., effector end-position) is adequate, or whether vision of the full limb is a boon. These are only a few possible questions. If effective, such an intervention has the potential to significantly improve rehabilitation outcomes. Though prior to the grand goal of altering rehabilitation practice, we need to also improve research practice.

5.1.2 Developing measures which capture the features of proprioceptive deficit that impact clinically meaningful outcomes

There is evidence to suggest that existing measures of proprioception used in clinical and research settings are lacking in a variety of ways: 1) measures isolate joints, measuring rotation on a single axis, 2) clinical measures lack sensitivity and/or suffer from ceiling effects making them useful solely in patients with deficits, and 3) multi-joint movements or posturing using planar robots limits movement to 2-dimensions.

In Chapter 2, we presented a novel tool for measuring proprioception that addresses these limitations, the full upper limb posture matching task (FULPM). Our preliminary results show promise, though larger samples will be needed to establish test validity. The measure was able to distinguish proprioceptive deficits/capacity in both healthy adults as well as stroke patients with reported difficulties with proprioceptive sensation. Though there were limitations and lessons learned.

The contralateral reference conditions, when the participant matched a limb to their pre-positioned opposite limb, did not appear effective. This was likely because the patients affected limb was either used to respond or used as a reference, either way resulting in similar posture matching error between limbs. The contralateral conditions will likely be removed from future testing, which is ideal since the current 4 trials per limb per condition seemed inadequate based on inter-trial variability within subjects. Moving forward I will need to assess what the ideal number of trials per condition is. It is possible that variability stemmed from differences in trial difficulty, though it could also be due to sensor noise. Additional testing will benefit from better control of or accounting for trial difficulty as well as validating the sensor setup using a gold standard such as optical motion capture.

We expected worse performance during the passive movement conditions, though we did not see a large difference between passive and active movement. This is likely due to inadvertent tactile feedback resulting from experimenter contact. This is difficult to avoid given the need for the experimenter to move a limb into varied postures. It is also possible that visual cues from the dummy helped patients. Before removing the passive condition, I will need to test whether removing dummy cues during the passive condition results in the expected increase in error. If it does not, then it may be best to stick to active movement.

In the existing FULPM paradigm, participants are instructed to match the posture of the tested limb to the reference posture. However, past research has shown that individuals are better able to judge bodily position when trying to discern effector end-position rather than joint angles (Fuentes & Bastian, 2009). It is unclear whether the same applies to multi-joint postures. A further experiment looking at effector end-position versus multi-joint posture may be informative in modifying the FULPM task.

Lastly, it is possible that motor tasks, such as the VR tasks presented in Chapter 3, could serve as a proxy for sensorimotor deficits. In Chapter 2 we compared the FULPM task to four traditional measures of proprioception. It is still necessary that I compare the FULPM to other traditional measures, namely, joint angle matching and planar robot paradigms, though from our preliminary data, we found little agreement between the traditional measures. However, 4 of 5 participants showed significant declines in performance with their affected limb when performing without visual feedback, which showed the expected association with FULPM error as well.

Performance under varied feedback conditions and across numerous tasks with unique demands could provide useful information regarding how deficits might be affecting an individual and their everyday activities.

5.1.3 Establishing a better understanding of how/when neural injuries manifest as proprioceptive deficit

Predicting functional deficit based on lesion analysis is a highly active field of research, and a difficult endeavor. For example, a lesion to the posterior parietal cortex can lead to a plethora of sensorimotor deficits given its diverse role in sensory integration and motor planning and control. Though as is stands, we have a limited understanding of the neural networks involved in complex action, such as grasping under distinct sensory feedback conditions, including grasping with or without vision of the limb. Creating these conditions in an fMRI scanner is also difficult; we can’t rely on virtual reality.

In Chapter 4, we addressed this by developing a fMRI paradigm that allows for selective removal of visual feedback of the limb without removing vision of the grasp object. This work in healthy adults was designed to answer basic gaps in knowledge regarding the network involved in human grasp. As it stood, research in human and non-human primates relied on either full vision or no vision at all (of the limb or object), which could be construed as grasping while reliant on memory of the object. It was unclear whether there were regions of the established frontoparietal visual grasp network that activated preferentially when grasping without visual feedback of the limb.

We were successful in identifying subregions of the frontoparietal grasping network which activate most strongly when grasping without vision of the limb. These results corroborate past research findings and assertions regarding the nature and function of proprioception. Similarly to prior research in macaques we identified regions that activate most robustly when vision is of the limb is present, those that activate equally with or without vision of the limb, and those that activate most robustly when vision of the limb is absent. Surprisingly, every region of interest (IPS, BA6, SMA, SPOC, IFG) showed a subset of voxels that activated most robustly without vision of the limb. A further surprise was that we found robust activity when grasping without vision of the limb that started in SPOC and continued ventrally along the midline of the occipital cortex. We can only speculate on why this might be. It is possible that the change in multi-sensory processing results in recruitment of typically visual oriented regions, though it could be an effect of task difficulty and/or attention (the participant actively trying to see their limb). Further, this work supported past assertions that proprioceptive processing is distributed across the brain, rather than there being a focal region with a predominant proprioceptive role. This aligns with evolutionary theories of proprioception which suggest that proprioception developed well before vision and is, perhaps more so than vision, interlinked with motor behavior. Given that many neuroscientists posit that the brain evolved to enable action, it makes intuitive sense that proprioceptive processing would transcend most all sensorimotor regions linked with a given behavior. Of course, this is highly speculative, but worth considering.

While there was no region of interest that showed predominant proprioceptive activation, there was a non-significant trend suggesting IPS and BA6 may be of especial importance in the non-visual control of grasp. While a larger sample might have identified a significant effect in IPS and BA6, we would never-the-less, be limited to drawing conclusions based on correlations (as is always the case with fMRI). It may be more informative to use transcranial magnetic stimulation (TMS) to disrupt regions at various points during grasp control and under varied feedback conditions (i.e., full feedback and no feedback from the limb), allowing us to simultaneously make claims of regional causality.

This work will be of utmost importance if we hope to make accurate predictions of deficit based on neural injury. A better understanding of the functional relevance of brain injury could also help develop individualized plans for treatment.

5.1.4 Discerning the overlap and disparity between proprioceptive modalities

The FULPM task assesses position, though those positions are assumed through movement, whether active or passive. The traditional measures of proprioception we tested in Chapter 2 measured a variety of proprioceptive features, including movement sense and position sense. Though, given the disagreement across these traditional measures, it is difficult to say how movement sense and position sense are similar or distinct. With greater sample sizes and more rigorous alternative measures, it may be possible to develop an understanding of how proprioceptive modalities relate and how each might uniquely predict functional outcomes. It is possible that a patient “profile” including weight sense, posture sense, and movement sense, provides the best prediction of outcomes. Further, it may be possible to associate deficits in each modality with specific neural injuries, though given the distributed nature of proprioceptive processing, I doubt it would be so straight forward.

While the studies in this dissertation did not attempt to address proprioceptive modalities, it is worth mentioning in terms of future research. In addition to comparing the FULPM task to additional measures of position and movement sense, I plan to also explore the sense of weight, effort, and force. In section 5.1.5, I will discuss patient experiences living with proprioceptive deficit. One patient reported frequently dropping objects, which they felt was attributable to proprioceptive sense. Of course, this could also be influenced or driven by weakness and/or tactile sensation deficits. If proprioception is involved, it could be due to inaccurate position sense and/or weight, effort, or force sense impairments. Bringing all modalities together, alongside tests of tactile sensation, are necessary if we hope to build an accurate understanding of typical and impaired sensorimotor performance, including performance outside of the lab.

5.1.5 Relating what we discover in our lab-based assessments of proprioceptive deficit and its effect on performance to "real-world" outcomes

This may be one of the most important lines of inquiry. Discerning what degree of deficit or change on a measure will result in noticeable and clinically meaningful change in a patient's everyday life is. It is obviously important in shaping rehabilitation practice and absolutely up to rehabilitation scientists to establish.

One way in which I plan to address this is using wearable sensors. These devices can be used to acquire simple metrics such as limb usage and intensity of use, as well as interlimb differences. Recent work from myself and colleagues has shown the potential of motion data from wearable devices in recognizing activities of daily living, such as activities involved in cooking, dressing, and cleaning (Chen, Baune, Zwir, Wang, & Wong, *In Press*. Comparing proprioceptive deficits, sensorimotor performance, and limb usage and intensity across distinct activities would give us one of the most objective looks at the real-world impact of stroke to date. Considering these deficits alongside other factors, such as hand dominance, age, mobility, and many more, may be most useful in tailoring individualized treatment plans, which has become an idealized goal in medicine that is difficult to execute given limited resources.

Such studies are planned, however, there is some data that wasn't presented formally in Chapters 2-4 that can give a better understanding of real-world outcomes in the present patients. I collected several measures assessing disability, participation, quality of life, and patient experiences. The measures are described below, as well as the results from the present five stroke patients. Figure 5.1 shows the difference in proprioceptive deficit between each patients reported most affected limb and unaffected limb (all reported significant impairment of the right limb). In brief, patients 1-4 exhibited greater error in the expected limb based on their report of unilateral deficit. As mentioned before, patient 5 did not show the expected pattern of deficit, for several possible reasons.

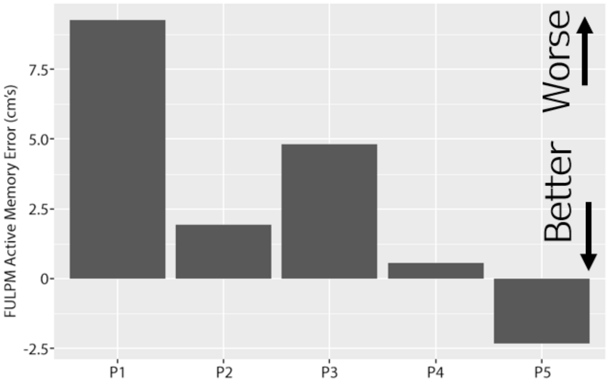

Figure 5.1. Affected – Unaffected FULPM error (Active Memory condition). Worse represents greater error with the reported affected limb.

Disabilities of the Arm, Shoulder, and Hand (DASH). The quick DASH, a shortened variant of the DASH (Institute for Work and Health, 2006), was collected to assess upper-limb disability. Results can be seen in Figure 5.2.

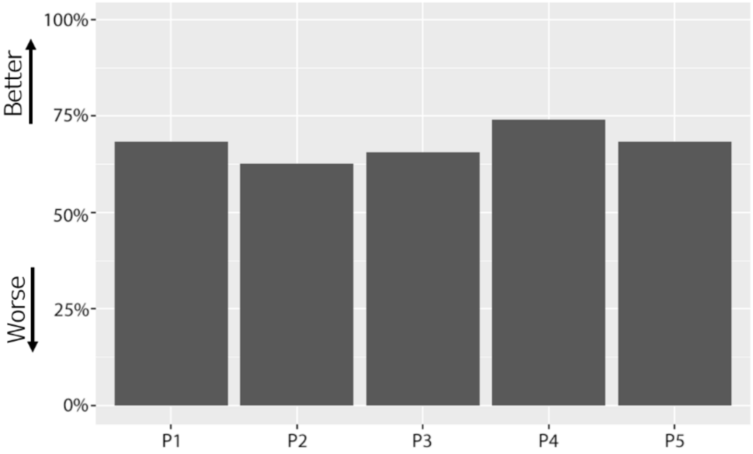

Figure 5.2. The quick-DASH.

There was no noticeable trend between FULPM error and disability. This is likely due to the fact that tasks on the quick-DASH can mostly be accomplished with one limb and the measure does not ask participants to report on each limb individually.

Ability to Participate in Social Roles and Activities (from the Quality of Life in Neurological Disorders (Neuro-QoL)). The Neuro-QoL is a collection of measures assessing various outcomes, including the Ability to Participate in Social Roles and Activities. Results can be seen in Figure 5.3. There was no obvious relationship between proprioceptive deficit and this measure of participation. It is likely due to the wide range of questions within. For example, "I can keep up with my work responsibilities" seems more likely to be affected by proprioceptive deficit, depending on the work, than "I am able to socialize with friends." As more data is collected, it will be important to analyze individual item responses to ascertain which aspects of participation are most affected.

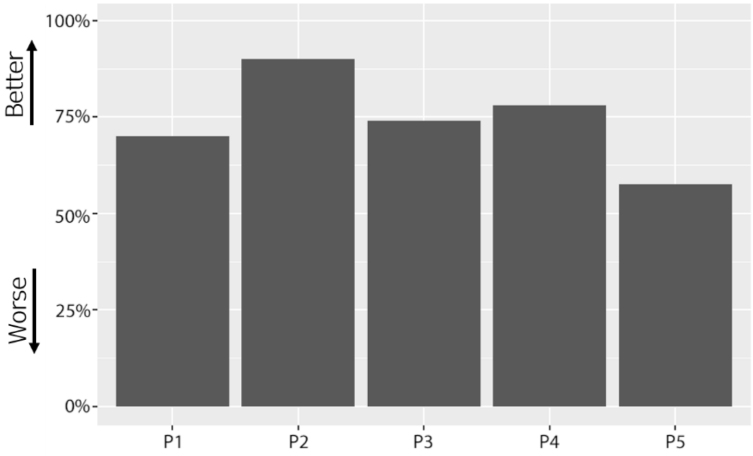

Figure 5.3. Ability to Participate in Social Roles and Activities. Scores are shown as a percentage of the possible maximum.

Upper Limb Proprioceptive Deficits Questionnaire (UL-PROP). The UL-PROP was designed in house as a potential screen for upper-limb proprioceptive deficit. It includes questions chosen based on the observed and theorized outcomes of proprioceptive deficit found in the literature. Responses to questions are given on a 5-point Likert scale (Strongly Disagree,

Disagree, Undecided, Agree, Strongly Agree), one rating per limb. Example questions include: "I have a difficult time knowing where my left/right limb is or how it is positioned if I cannot see it" or "I watch or monitor my left/right limb when using it." Results can be found in Figure 5.4.

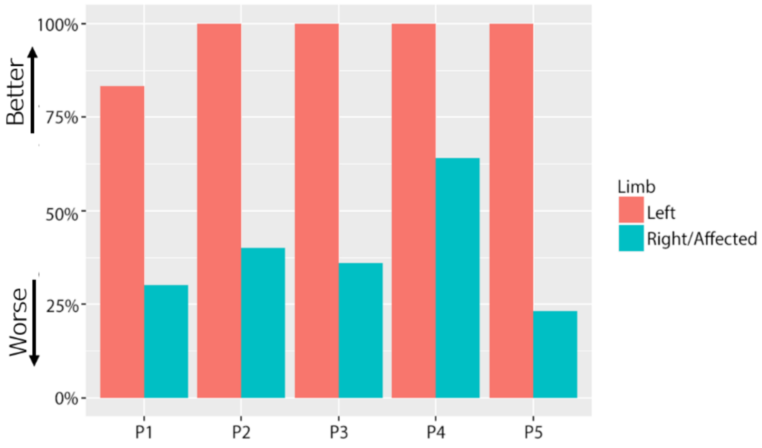

Figure 5.4. Upper Limb Proprioceptive Deficits Questionnaire (UL-PROP).

For patients 1-4, if ordered from worst to best on both the UL-PROP and FULPM task, there is perfect agreement. However, patient 5 shows perhaps the worst score of the patients for their right limb, despite worse performance for the left limb on the FULPM task. It is possible that this patient experiences bilateral proprioceptive deficit alongside additional motor deficits or weakness of the right limb, leading them to focus on the right limb's deficits. Per recommendation, measures of grip strength and apraxia were included starting with patient 5 to help account for comorbidities. Since I do not have these measures on the first four patients a comparison isn't useful, though as more data is collected, I can explore what factors might explain patient 5's unique outcomes.

Proprioception and Rehabilitation Experiences Interview. A series of in-house questions were developed to structure informal interviews with patients at the end of their study session. The questions ask the patients to describe their experiences in rehabilitation, their awareness of proprioceptive deficits, and if they are aware, how they feel they have impacted their performance and participation in everyday activities.

The interview was developed in response to an absolute absence of literature covering patient phenomenology and awareness of proprioceptive deficits. Because we often do not have to focus on proprioception, it was unclear whether deficits are obvious to patients and how they have impacted them personally.

What we found was that all patients had undergone inpatient and outpatient therapy, including physical and occupational therapy. They also reported being taught to rely on vision to monitor their affected limbs. One patient reported being trained to walk without relying on vision, akin to my plans for retraining with the upper limb, though this approach hadn’t been taught for the upper limb. All reported being acutely aware of the changes in their proprioceptive capacities: the ability to detect position and movement. They reported feeling that these deficits did impact them negatively. One reported having burned their hand repeatedly while cooking and another reported that they are frequently knocking over or dropping objects.

This approach of informal interviews can, if anything, help guide future questions and experiments. It will be interesting to see whether patient report of proprioceptive deficit closely matches our lab-based measures of proprioceptive capacity/deficit.

5.2 Lessons learned

This dissertation presents a number of novel findings and lessons. Most notably, researchers should take caution in drawing conclusions without strongly considering the tasks used, since the task in part determines what sensory information is relevant to successful performance. Chapters

2 and 3 both provide evidence that stroke patients with proprioceptive deficits are reliant on visual feedback during reaching type tasks; as suggested by previous research (Section 1.2.2), this reliance is likely detrimental to recovery. We also saw that this reliance isn't universal but depends on the task at hand (Figures 3.8 and 3.9). More specifically, only one patient showed major deficit with their affected limb in the reach-to-press task when vision was removed, though four showed major deficit in the tracing task. Our results suggest that the disparity in past study conclusions may be attributable, at least in part, to differences in study paradigms. Without comparing performance across several tasks, it is difficult to draw meaningful generalizable conclusions and we also risk missing out on important factors influencing performance. We also saw that an alternative measure of proprioception (the FULPM task) looking at multi-joint upper limb postures may be a valid alternative in clinical and research settings, though further validation is needed. The value of proprioceptive research is strongly limited by the validity of its measures, and we demonstrate a novel approach that improves upon past measures in several meaningful ways. This is but one piece of a greater effort that is needed to understand the relationship between proprioceptive modalities and clinically meaningful outcomes. Lastly, we provide the first evidence in humans of activity in the human frontoparietal grasping network specific to non-visually guided grasp. This was a needed addition given the potential confounds introduced by past research paradigms. These results should guide future study of the neural correlates of proprioception, especially in trying to ascertain regions with significant clinical relevance and regions involved in behaviors of interest.

Generally, Chapters 2 and 3 demonstrate the immense utility that virtual reality offers to both clinical settings and in research, especially in sensorimotor control and specifically proprioception research. While alternative approaches to manipulating bodily feedback require visual blinds and other manipulations that decrease the tasks' ethological validity, virtual reality allows for easy manipulation of vision on demand and minimal repercussions to the task. We also demonstrate the validity of VR research by comparing VR task performance to a non-VR task. At a group level, patients showed significantly poorer performance on the non-VR motor task, the Box and Block task. The Box and Block results are shown in Figure 5.5. It is possible that decline without vision was also due to tactile deficits. In our Box and Block paradigm, participants performed as usual with full vision, and then again with all lights turned off. That means vision of the blocks were also absent and all participants would have to grasp the objects relying on haptic exploration. However, the results from the VR tasks in Chapter 4 show a similar pattern, despite requiring no tactile feedback to perform Therefor, it is likely proprioceptive deficit is a major contributing factor. The tasks presented in this dissertation are only a few of many potentially useful tasks. Moving forward, my goal is to find a way to incorporate objects and person-object interactions within virtual reality. This would allow manipulation of both the participants bodily feedback as well as their environment and allow for the development of much more complex and ethologically relevant tasks and assessments.

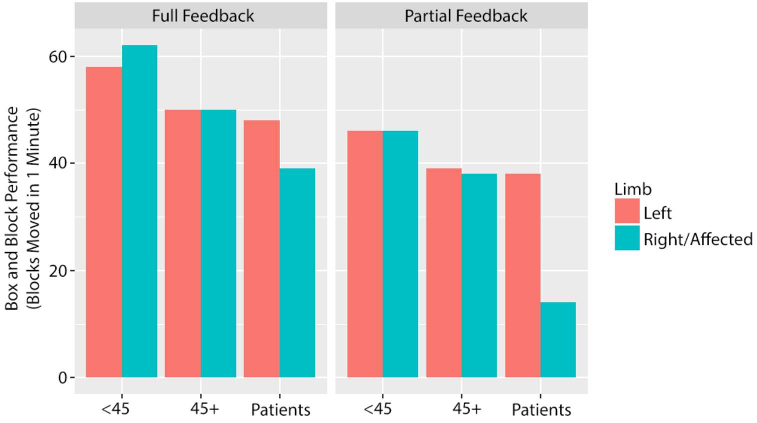

Figure 5.5. Box and Block task.

The presented preliminary data, despite small samples, have uncovered numerous useful modifications and future lines of research, both relevant directly to the tasks demonstrated as well as to much broader gaps in our understanding of sensorimotor control. Stroke rehabilitation is difficult given the nature of the injury. The brain may be plastic, though less so the older we get, and stroke becomes much more likely as we age. Targeted sensorimotor interventions have received little attention, both in practice and in research. Though alongside previous studies, the presented evidence suggests that interventions that target proprioception have the potential significantly improve post-stroke outcomes. While this work focuses on stroke survivors, the same principles may apply to other patient populations with proprioceptive deficit, such as traumatic brain injury patients, peripheral nerve injury, and Parkinson’s Disease. This work points towards a seemingly endless line of questions and experiments with the potential to make a large impact in advancing basic knowledge and rehabilitation practice.

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