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The Neuroanatomical Correlates of Impaired Position Sense After Stroke

by

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## **Abstract**

Proprioception describes our sense of self-position and movement without vision. It plays a key role in the production and control of movement. Affected in 50% of stroke patients, impairment in proprioception is correlated with poor motor recovery, functional outcomes, and extended hospitalization. Proprioception-targeted rehabilitation is lacking. To contribute to improved understanding of the anatomical regions underlying proprioception, this study aimed to identify brain areas responsible for impaired position sense post-stroke. Voxel-based lesion-symptom mapping compared lesion location and performance on quantitative robotic position sense assessment. This and region of interest analyses revealed that the hypothesized areas: the thalamus; posterior limb of the internal capsule; postcentral gyrus; posterior parietal association area were associated with poor position sense in addition to non-hypothesized areas: insula; lingual, inferior frontal, superior temporal, and middle temporal gyri. Position sense appears to be a multi-dimensional construct, processed via a distributed network of brain regions.

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## List of Symbols, Abbreviations and Nomenclature

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A	Ambidextrous
ACA	Anterior cerebral artery
Ant CH	Anterior choroidal artery
BIT	Behavioural Inattention Test
CAT	Computed axial tomography
CMSA	Chedoke McMaster Stroke Assessment
CST	Corticospinal tract
CT	Computed tomography
DWI	Diffusion weighted (MR sequence)
F	Female
FDR	False discovery rate
FIM	Functional independence measure
FLAIR	Fluid-attenuated inversion-recovery (MR sequence)
fMRI	Functional magnetic resonance imaging
L	Left
M	Male
MAS	Modified Ashworth Scale
MCA	Middle cerebral artery
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
NPM	Non-parametric mapping
P2	Branch of the posterior cerebral artery
PCA	Posterior cerebral artery
PLIC	Posterior limb of the internal capsule
PoCG	Postcentral gyrus
PPAA	Posterior parietal association area
PPC	Posterior parietal cortex
R	Right
RESTART	Rehabilitation, Stroke deficits and Robotic Technology
ROI	Region of interest
SPM8	Statistical parametric mapping (version 8)
Symbol	Verbatim
TLT	Thumb Localizing Test
VLSM	Voxel-based lesion-symptom mapping
VPL	Ventral posterior lateral nucleus of the thalamus

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## Chapter One: **Introduction**

### **1.1 Purpose**

The aim of this study is to determine which brain regions are associated with decreased upper extremity position sense resulting from stroke. Doing so will contribute to improved understanding of the anatomical regions underlying proprioception.

### **1.2 Background**

Proprioception describes the sensory information that results in a sense of self-position and movement without the use of vision (Sherrington, 1907). Proprioception plays an important role in the initiation and control of limb posture and movement (Sainburg, 1995; Scott, 2002). It is reported to be impaired in up to 50% of stroke patients (Carey et al., 1996; Connell et al., 2008; Dukelow et al., 2010). Such sensory deficits are thought to correlate with poor motor recovery of the affected upper extremity after stroke (de Weerd et al., 1987; Mercier et al., 2004; Pavot et al., 1986; Wade et al., 1983) and have been linked to impaired function resulting in longer inpatient stays and increased care requirements upon discharge (Chester and McLaren, 1989; Davidoff et al., 1991; Zeman and Yiannikas, 1989). Despite this, stroke rehabilitation places far less emphasis on sensory impairments than motor deficits. Recent systematic reviews concluded that quality studies and gold standards are lacking in the areas of sensory assessment and intervention following stroke (Connell and Tyson, 2012; Doyle et al., 2010; Schabrun and Hillier, 2009). This is a dilemma for rehabilitation: if impaired sensation impacts motor performance, are we missing the mark by not providing treatment aimed at sensory processing?

At the root of this question is the fact that the central neural mechanisms underlying upper limb proprioception in humans require further research. An issue impacting studies in this area is that of measurement. Typical clinical proprioception assessments tend to use observer-based ordinal scales. Such scales tend to be coarse and therefore hinder accurate quantification of deficits or identification of subtle, but clinically relevant changes, over time. Further clinical assessments of proprioception have been found to have poor reliability (Lincoln et al., 1991; Lincoln et al., 1998), sensitivity (Connell and Tyson, 2012), and standardization (Connell and Tyson, 2012). In the absence of reliable identification and quantification of deficits, it is not possible to advance our understanding of the problem and develop appropriate treatments. To address this, we have previously developed a reliable, valid, and sensitive method to quantify proprioception using robotic technology. This project combines robotic assessment of proprioception and brain lesion analysis to identify areas responsible for poor position sense after stroke. The findings will provide a foundation for further work to improve assessment and treatment for stroke patients.

### **1.3 Literature Review**

#### ***1.3.1 Proprioception in the Upper Limb***

##### **1.3.1.1 Proprioception**

Proprioception is the perception of position, motion, and force generated by the body based on sensory information from the periphery (Sherrington, 1907). This afferent information is critical for effective motor control as it contributes to postural control, joint stability, coordination, and some conscious appreciation of limb position and movement (Cordo et al., 1994; Niessen et al., 2008; Porter and Lemon, 1993). Case studies have revealed that people with proprioceptive loss exhibit poor motor control even if they have intact motor systems and are using vision. These

individuals are unable to produce coordinated multi joint movements (Jeannerod et al., 1984; Sainburg, 1995) or perform extended movement sequences (Rothwell et al., 1982). They lack accuracy when reaching (Gordon et al., 1995; Messier et al., 2003) and are unable to sustain a constant level of muscle contraction without vision, making fine motor tasks such as fastening buttons or writing extremely difficult (Sanes et al., 1985). Proprioception is traditionally thought to be comprised of two subcomponents: position sense (awareness of limb position) and kinaesthesia (awareness of passive or active movement) (Sherrington, 1907). The contemporary definition also typically includes sense of effort (an efferent copy of the motor command resulting in the feeling of movement) (Gandevia et al., 2006; Goble, 2010; Riemann and Lephart, 2002).

#### 1.3.1.2 Position Sense and Kinaesthesia

Clinicians tend to be interested in both position sense and kinaesthesia and consider these subcomponents of proprioception to be distinctly different. Both senses arise from peripheral receptors in muscle, joints, and skin. Despite this common origin, various studies have detected differences in the perception of position sense and kinaesthesia. Muscle spindles are powerfully stimulated by vibration and it has been demonstrated that higher vibration frequencies induce the feeling of movement whereas lower frequencies result in a perceived position change (McClosky, 1973). Similarly, externally applied movements that progressively slow down result in a sense of movement that eventually fades into a sense of position change (Clark et al., 1985). Studies such as these provide insight into the perceptible differences between position sense and kinaesthesia, but how the neural system differentiates them remains less clear.

### 1.3.1.3 Position Sense: Peripheral Neurophysiology

The term “proprioceptors” describes the peripheral sensory organs (muscle spindles and Golgi tendon organs) that convey information about limb position and movement to the central nervous system (Purves et al., 2008). However, the complex percepts of position sense and kinaesthesia have been found to require a combination of input from muscle spindles (Goodwin et al., 1972), cutaneous afferents (Edin and Abbs, 1991; Edin, 2001), Golgi tendon organs (Jami, 1992), and joint receptors (Ferrell et al., 1987). Of these, muscle spindles are considered the primary contributors to sense of limb position and movement while Golgi tendon organs, joint and skin receptors play a lesser role (Gandevia et al., 1992; Matthews, 1982; McCloskey, 1978; Williams, 1981).

The composition of muscle spindles enables them to signal muscle length change and rate of change. These sensory receptors are comprised of three types of intrafusal fibres: nuclear chain, dynamic nuclear bag, and static nuclear bag fibres (Latash, 2012). When these intrafusal fibres are stretched, the sensory nerve endings attached to them also stretch and their firing rate increases. Large diameter (1a) afferents arise from all three intrafusal fibre types. They respond to sudden stretching, have rapidly adapting responses to muscle length change, and are thought to transmit information about velocity and direction of movement (Purves et al., 2008). As such, they are considered the principle receptors for both position sense and kinaesthesia (Pearson and Gordon, 2013). Secondary muscle spindle endings (II), which arise from nuclear chain fibres and static nuclear bag fibres (Pearson and Gordon, 2013), are slower to respond to sudden stretch and produce sustained responses to constant muscle lengths. Thus they are thought to provide information about static limb position (Pearson and Gordon, 2013). Intrafusal fibre sensitivity is

adjusted by gamma motor neuron innervation. Dynamic gamma motor neurons increase the sensitivity of 1a fibres and static gamma motor neurons act on both the 1a and II fibres (Pearson and Gordon, 2013). This mechanism enables the intrafusal fibres to provide information during muscle contraction (Latash, 2012) and provides a site for modulation by higher brain centres (Gardner and Johnson, 2013).

#### 1.3.1.4 Position Sense: Central Processing

The large, rapidly conducting fibres that carry proprioceptive and cutaneous information travel together into the spinal cord. In the dorsal horn the large proprioceptive 1a axon bifurcates into ascending and descending branches (Amaral, 2013). The descending branch travels several spinal segments, synapsing on lower motor neurons to mediate segmental reflexes (Gardner and Johnson, 2013; Purves et al., 2008). These synapses contribute to the subcortical reflex pathways that are largely responsible for regulating proximal muscle activity (Pearson and Gordon, 2013). The remaining proprioceptive and cutaneous afferents ascend the spinal cord.

There is general consensus that proprioceptive information ascends the spinal cord in both conscious and non-conscious routes. That is, “conscious” routes eventually project to the cortex and have the potential to be consciously perceived. Further, the availability of this information at the cortical level is essential for initiating and programming commands requiring precise voluntary movement control as is essential for performing activities of daily living (Pearson and Gordon, 2013). Alternatively, proprioceptive information travelling in “non conscious” routes terminates in the cerebellum or brainstem and provides critical sensory input to the subcortical pathways that are largely responsible for regulating proximal musculature (Lisberger and Thach,

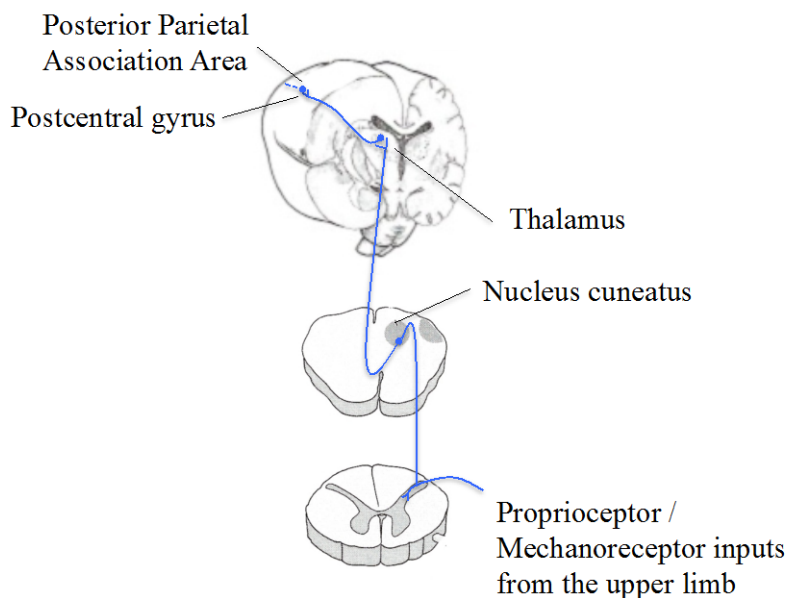
2012; Pearson and Gordon, 2013). This multi-pathway organization is thought to reflect the important role that proprioception plays in feed-forward, online, and feedback aspects of motor control (Latash, 2012; Pearson and Gordon, 2013; Riemann and Lephart, 2002; Scott, 2012; Sultan et al., 2012).

Conscious appreciation of proprioceptive and cutaneous information is attributed to the dorsal column/medial lemniscal system (Felton and Shetty, 2010; Gardner and Johnson, 2013; Purves et al., 2008). Sensory axons from peripheral proprioceptors enter the dorsal root ganglion of the spinal cord and then ascend somatotopically in receptor-specific zones of the dorsal columns. The upper limb afferents synapse in the nucleus cuneatus at the level of the medulla. The fibres then cross midline, to ascend in the medial lemniscus to the ventral posterolateral (VPL) nucleus of the thalamus. Projections from this area travel through the posterior limb of the internal capsule to Brodmann's areas 3a and 2 of the primary somatosensory area in the parietal cortex (Amaral, 2013; Gardner and Johnson, 2013). As primary somatosensory areas, these regions are involved in detection, localization, and discrimination of somatosensory information.

Specifically, area 3a primarily receives muscle spindle input to process information about limb position while area 2 combines this and cutaneous information to facilitate hand posture, grip force and tactile object recognition (Amaral, 2013; Gardner and Johnson, 2013; Krubitzer et al., 2004). These areas and the remaining primary somatosensory divisions then project to Brodmann's area 43 (secondary somatosensory area) and areas 5 and 7 for integration with inputs from other cortical areas (Gardner and Johnson, 2013; Purves et al., 2008). The secondary somatosensory area provides a higher order level of processing and plays a role in focusing attention on somatosensory stimuli which is likely important for efficient reach as well as object

manipulation (Chen et al., 2008; Gardner and Johnson, 2013; Hoechstetter et al., 2000).

Brodmann's areas 5 and 7 form the posterior parietal association area which has extensive cortical connections and integrates multiple sensations for use in guiding movement (Kandell, 2013). Area 5 updates the spatial map of body parts relative to each other and is involved in arm movements (Andersen and Cui, 2009; Kalaska et al., 1983), reach (Lacquaniti et al., 1995; Scott et al., 1997), and grasp (Baumann et al., 2009; Sakata et al., 1997). Area 7 receives more visual information and integrates this with proprioceptive information to process world referenced spatial coordinates used for reaching and skilled hand coordination (Andersen, 1997; Filimon et al., 2009; Pellijeff et al., 2006).



**Figure 1 Dorsal Column/Medial Lemniscal Pathway**

Proprioceptive afferent information from the upper limb enters the cervical spinal cord via the dorsal root ganglion. In the dorsal horn, fibres bifurcate, some enter the spinal grey matter and the remainder ascend in the dorsal columns. These fibres synapse at the nucleus cuneatus in the medulla then cross midline and are carried to the ventral posterolateral nucleus of the thalamus via the medial lemniscus. From there fibres pass through the internal capsule to the postcentral gyrus and the posterior parietal association area.

Such functions have been attributed to the histologically defined Brodmann's areas primarily through animal studies. In alive and awake humans, functional magnetic resonance imaging (fMRI) studies suggest that the human somatosensory cortex shares a similar organization (Bremmer et al., 2001; Culham and Valyear, 2006), however different nomenclature is used. In humans, the postcentral gyrus is described as the primary somatosensory area which generally corresponds to Brodmann's areas 3, 2, and 1 (Gardner and Johnson, 2013). The secondary somatosensory area in the upper bank of the lateral sulcus is considered the area 43 equivalent (Disbrow et al., 2000; Rizzolatti and Kalaska, 2013). The posterior parietal association area is comprised of the superior parietal lobule (Karnath, 2001; Scheperjans et al., 2008), medial wall of the intraparietal sulcus, posterior paracentral lobule, and the precuneus (Scheperjans et al., 2008). In patients, damage to the posterior parietal association area produces deficits in personal and extra-personal spatial perception, visuomotor integration, and selective attention thus providing insight into the complex function of this region (Kandell, 2013).

The insula appears to receive spatial information from the upper limb for higher-level processing. A fMRI study found that the anterior insula became activated when subjects were aware that they were causing a movement, while the inferior parietal lobe was active when they knew they were not causing the action (Farrer and Frith, 2002). Such connections are in keeping with another fMRI study that demonstrated linkages between the insula, parietal (3b, 2 and secondary somatosensory areas), and vestibular cortices (Fasold et al., 2008). The function of these connections is not completely understood. However, researchers tend to agree that the insula is involved in further processing of multimodal sensory information associated with voluntary movement to inform cognitive processes such as: body agency [feeling of ownership;

(Farrer and Frith, 2002)]; interoception [sense of the physiological condition of the body; (Berlucchi and Aglioti, 2010)]; or subjective feelings of one's current movements (Craig et al., 2009).

For completeness, it is noted that proprioceptive information essential for motor control also ascends the spinal cord via pathways that do not directly connect to the cortex. Animal studies have found that the pathways differ depending on whether the origin is the fore or hind limb (Grant, 1962; Oscarsson and Uddenberg, 1964). It is believed that humans share a similar organization (Proske and Gandevia, 2012). Thus the rostral spinocerebellar and cuneocerebellar pathways are credited with conveying proprioceptive information from the upper limbs (Gilman, 2002; Grant, 1962; Lisberger and Thach, 2012; Oscarsson and Uddenberg, 1964). In keeping with animal models, each pathway transmits specific aspects of proprioceptive information. The rostral spinocerebellar pathway transmits proprioceptive information resulting from active movements while the cuneocerebellar pathway is utilized whether the limb is moved passively or voluntarily (Bosco and Poppele, 1997; Lisberger and Thach, 2012). This is congruent with the theory that the cerebellum compares the actual and expected sensory consequences of movement. Proprioceptive information terminates in the vermis and intermediate zones of the cerebellum. The output from these areas adjusts posture and ongoing movements through influential connections with the descending motor tracts (Pearson and Gordon, 2013; Thach et al., 1992).

This study will investigate if damage in one of the structures receiving dorsal column/medial lemniscal input is correlated with poor position sense post stroke.

### ***1.3.2 Stroke***

#### **1.3.2.1 Background**

According to the Public Health Agency of Canada (2009) 50,000 Canadians have a stroke each year. A stroke is the result of an interruption of blood supply to the brain – either due to blockage of a blood vessel (ischemic stroke) or rupture of a blood vessel (haemorrhagic stroke) (WHO, 2005). In either case, impaired blood flow cuts off oxygen and nutrient supplies to the brain, resulting in tissue damage. Depending on the vessel and extent of damage, various clinical consequences may occur.

#### **1.3.2.2 Cerebral Blood Supply of Principle Somatosensory Areas**

Five arteries supply the subcortical structures important for transmitting and processing position sense information. The middle cerebral artery (MCA) supplies a large territory that encompasses important somatosensory regions. It perfuses the majority of the lateral surface of the cerebral hemisphere, including the somatosensory area of the parietal lobe, as well as the white matter for the hemisphere's convexity (Brust, 2013). The lenticulostriate arteries of the MCA supply the superior half of the posterior limb of the internal capsule through which sensory fibres travel to the cortex (Brust, 2013). Heinsius (1998) reported that a large MCA infarct results in a high incidence of sensory deficits, although the modalities affected were not specified.

Four other arteries also supply important regions for sensory processing. The anterior choroidal branches of the internal carotid artery supply the inferior portion of the posterior limb of the internal capsule (Mohr et al., 2004). The P2 branch of the posterior cerebral artery (PCA) gives rise to several small inferolateral arteries that perfuse the ventral posterolateral nuclei of the

thalamus (Schmahmann, 2003). Patients with damage to this area experience impairments of position and vibration sense among other deficits (Bogousslavsky et al., 1988). Finally, the posterior inferior cerebellar and superior cerebellar arteries supply the cerebellar zones that receive somatosensory input from the spinal cord (Tatu et al., 1996).

### 1.3.2.3 Stroke Rehabilitation

Stroke rehabilitation has not kept pace with the advances in the field of neuroscience. The theoretical foundations of classical treatment paradigms such as Bobath (1970), Brunstrom (1970), and proprioceptive neurofacilitation (Voss, 1967) were based on the physiological and hierarchical theories of motor development and neuroscience of their time. Despite varied theoretical bases and treatment approaches, none of these concepts have demonstrated definitive efficacy over the others (Basmajian et al., 1987; Kollen et al., 2009; Langhammer and Stanghelle, 2003; Logigian et al., 1983; Lord and Hall, 1986; Wagenaar et al., 1990). These approaches continue to be used clinically to varying degrees. The Brunstrom stages of recovery have become the foundation for the widely-used Fugl-Meyer Motor Assessment (Fugl-Meyer et al., 1975) and the Chedoke McMaster Stroke Assessment (Gowland et al., 1993). Further, although the Bobath concept is commonly taught in post-graduate rehabilitation courses, little has been published on its evolving theoretical framework (Brock et al., 2009).

Evidence-based medicine is emphasized in the education today's rehabilitation therapists, which has led to improved quality and increased numbers of neurorehabilitation studies. Such studies tend to focus on modality-based motor treatment strategies. Examples of these include: repetitive training (Cirstea et al., 2006), task-oriented training (Winstein et al., 2004), constraint-induced

movement therapy (Taub et al., 2003), mirror therapy (Altschuler et al., 1999), mental imagery (Page et al., 2005), movement observation (Ertelt et al., 2007), neuromuscular stimulation (Bowman et al., 1979; Chae et al., 1998), functional electrical stimulation [review (Pomeroy et al., 2006)], electromyographic feedback [review (Woodford and Price, 2007)], robotics (Lo et al., 2010a), acupuncture (Wong et al., 1999), repetitive transcranial magnetic stimulation (Takeuchi et al., 2008), and transcranial direct current stimulation (Hummel et al., 2005). In stark contrast, only a few studies have investigated the role of sensory interventions after stroke. This discrepancy was highlighted in recent reviews examining the evidence for sensory measures and sensory interventions in neurologic conditions (Connell and Tyson, 2012; Doyle et al., 2010; Schabrun and Hillier, 2009). Given the impact that proprioception has on motor recovery (section 1.2), the neurorehabilitation field would clearly benefit from improved understanding of the role of sensation, particularly proprioception, after stroke.

#### 1.3.2.4 Stroke Rehabilitation for Proprioceptive Deficits

Few studies have investigated treatments to promote sensory recovery after stroke despite the widespread clinical use of sensory stimulation to facilitate movement (Bobath, 1970; Brock et al., 2009) and decades of observational evidence that sensory deficits adversely affect functional outcome (Smith et al., 1983; Twitchell, 1957; VanBuskirk and Webster, 1955; Zeman and Yiannikas, 1989). A variety of somatosensory treatment interventions for the upper extremity have been investigated including those with a focus on tactile, stereognostic, and proprioceptive perception. The degree to which improvement in one somatosensory domain (e.g. tactile discrimination) generalizes to others is unclear with studies reporting both good (Yekutieli and Guttman, 1993) and unlikely (Carey et al., 1993) generalization. Such varied findings may be

related to the outcome measures used, but raise suspicion that research for specific somatosensory domains may be worthwhile.

Five studies were identified that aimed to investigate treatments specifically targeted at upper extremity proprioceptive deficits. In four of these studies, limbs or single joints were passively placed in a position and the stroke subject replicated or described the position with visual and/or therapist feedback used to promote improved position sense when necessary (Carey et al., 1993; Carey et al., 2011; Smania et al., 2003; Yekutieli and Guttman, 1993). Each of these studies reported moderate improvements in position sense. The fifth study investigated the effects of intermittent pneumatic compression and found it to have a somewhat positive impact on proprioception as measured with the kinaesthetic subcomponent of the Nottingham Sensory Assessment (Cambier et al., 2003). Interestingly, sensory inputs such as vibration, weight-bearing, or mobilization which would seemingly influence peripheral proprioceptors, and which are used clinically to influence movement, (Lennon et al., 2001) have not been systematically examined in well controlled studies.

### ***1.3.3 Assessment of Proprioception***

#### **1.3.3.1 Clinical Assessment of Proprioception**

The occurrence of proprioceptive deficits after stroke has been reported to range from 36% to 54% (Carey et al., 1996; Reding, 1990) and is linked to poor functional return in the upper extremity (de Weerdt et al., 1987; Kuffosky et al., 1982; La Joie et al., 1982; Wade et al., 1983). This wide range may be related to a few factors. To start, studies do not always use the same definition and means of assessing “proprioception”. In two oft-cited papers (Carey et al., 1996;

Lincoln et al., 1991) the importance of proprioception and examples of its functional relevance are provided, however, neither clearly define the components of proprioception (static or movement sense) that they are assessing. Lincoln's proprioception assessment includes 3 subcomponents (finger finding; positional mimicry; distal proprioception) while Carey's has only 1 component (wrist position sense). Lack of clarity as to which components of proprioception are measured, how they are measured, and the location tested may be factors in the wide range of incidence of proprioceptive deficits reported after stroke.

The range of deficits reported may also be related to the tools and methods used to assess proprioception. A common clinical evaluation of position sense is the thumb localization test (Hirayama et al., 1999). Another is based on the ability of a patient to identify the upward or downward position of a passively placed proximal joint (Lincoln et al., 1991), finger (Bickley and Szilagyi, 2007), or toe (Bickley and Szilagyi, 2007). Kinaesthesia may be assessed in a similar manner: the patient's ability to correctly identify the presence and direction of movement as a joint is flexed or extended (Bentzel, 2007). Often these proprioceptive components are assessed as part of a larger evaluation of sensory function (Connell and Tyson, 2012).

Though commonly used, these clinical assessments have inherent limitations. In an attempt to quantify proprioception, percentages (Bentzel, 2007) or ordinal scales are used (Lincoln et al., 1991). In either case, performance measurement is ultimately based on observer-based interpretation. In addition, ordinal scales have been found to have poor inter-rater reliability, poor normative value criteria, and lack sensitivity (Carey et al., 1996; Connell and Tyson, 2012; Garraway et al., 1976; Lincoln et al., 1991). Connell et al (2012) acknowledged the importance

of inter-rater reliability in clinical settings where patients may be tested by several raters over the course of their rehabilitation. They found that inter-rater reliability can be improved with careful standardization and detailed operating instructions.

More quantitative assessments of proprioception have been proposed for use in the stroke population (Carey et al., 1996; Leibowitz et al., 2008). However, these methods are rarely used in either clinical or research applications, perhaps because they assess position sense at a single joint (Carey et al., 1996) and require manual repositioning of the limb (Carey et al., 1996; Leibowitz et al., 2008). These assessments also are time-consuming to administer.

#### 1.3.3.2 Robotic Position Sense Assessment

Robotic technology has been applied to retrain motor control after stroke for a number of years (Fasoli et al., 2003; Lo et al., 2010a; Volpe et al., 1999), however, its use as an assessment tool is relatively new (Colombo et al., 2010; Dipietro et al., 2009; Dukelow et al., 2010; Simo et al., 2011). Robotic assessment after stroke has several advantages over typical clinical assessments. First, it produces quantifiable and highly reliable measures. Second, robots are capable of controlling limb movement and producing consistent targets while controlling other parameters such as the inflow of visual information (Scott and Dukelow, 2011). Third, results of robotic assessments can be compared to normative data like blood tests. This is something that is uncommon for rehabilitation assessments. Lastly, robotic technology is able to detect subtle changes in movement trajectory and velocity and may provide quantifiable resistance (Simo et al., 2011). In summary, robotics allow for a level of precision and accuracy not previously possible with the observer-based ordinal scales typically used to measure proprioception.

A recent study developed and validated a robotic assessment of limb position sense in patients with stroke (Dukelow et al., 2010). This position match task has several advantages. First, it is objective and is not subject to human interpretation. It is able to detect subtle deficits, which may not be identified clinically. Second, this task produces continuous measures, which do not appear to have ceiling or floor effects. This is in contrast to the current clinical tests which suffer from poor reliability, sensitivity, and lack good quantification (Carey et al., 1996; Lincoln et al., 1991). The range of scores inherent in continuous measures is expected to prove useful in quantifying variable deficits of position sense. Third, this test has a large normative data set that permits statistical comparisons for age, sex, and handedness with matched controls. Fourth, the variability parameter demonstrated agreement with the Thumb Localizing Test ( $p < 0.001$ ). Finally, the robotic position match task has demonstrated excellent test-retest reliability for two parameters and good test-retest reliability for the third. In summary, the robotic test of position sense provides us with an assessment tool that provides accurate measurement of position sense deficits after stroke. Our study will use this quantitative position matching assessment in combination with stroke lesion analysis to better understand the neural correlates of position sense.

### ***1.3.4 Locating Behaviour in the Brain***

#### **1.3.4.1 Origins of the Lesion Analysis Method**

Linking specific behaviours to locations in the brain has long been a pursuit of neuroscientists. This quest has evolved greatly over the past century and a half. In the 1860's Paul Broca pioneered the 'lesion method' by examining the brain of a patient posthumously to identify the

area of damage responsible for aphasia. Although he was not the first to relate language to the left hemisphere, his finding launched a new approach to localizing brain function.

#### 1.3.4.2 Use of Imaging for Lesion Analysis

Much more recently, lesion analysis evolved to overlay plots of brain images from patients with hemispatial neglect following stroke (Vallar and Perani, 1986; Weiller et al., 1993). Using this technique, computed (axial) tomography (CT or CAT) scans or magnetic resonance imaging (MRI) scans of individuals with a specific disorder are transferred onto brain template drawings to show common areas of damage (Brett et al., 2001). The area of overlap is related to the deficit and is hypothesized to be required for the normal function. An obvious advantage of these modern techniques is that they can be conducted with living subjects. Another advantage of this technique is that it permits several individuals to be compared at the same time and is therefore more apt to be generalizable to the greater population than single case studies. However, the overlay method faces the following criticisms. First, inference of the brain lesion required for a particular function is made without statistical support (Rudrauf et al., 2008a). Second, brain injury is not random and certain areas of the brain are more vulnerable to injury than others (Caviness, 2002; Heinsius et al., 1998). Further, in order to make group comparisons, the individual brains need to be transformed to a common stereotaxic space to accommodate for individual differences in shape, size, and structure (Amunts et al., 2004). Despite these limitations, this technique, much like that of Broca, has provided refined our understanding of the where and how behaviours such as language functions and neglect are processed (Bates et al., 2003; Karnath et al., 2011).

#### 1.3.4.3 Functional Magnetic Resonance Imaging (fMRI)

Another technique developed for correlating brain structure and function, fMRI, was developed in 1990 (Ogawa et al., 1990). This technique identifies regional blood flow patterns, indicating areas of activation (Le Bihan, 2003) and thus identifies brain regions involved in a specific behaviour in healthy subjects or patients. Functional MRI has been used to demonstrate reorganization of cortical areas in the stroke population (Stinear et al., 2007; Ward et al., 2003). However, certain characteristics of fMRI limit its use in defining stroke lesion location. For instance, due to the distributed nature of behaviour, brain regions may be active but not directly required for a specific function (Price et al., 1999). Also, white matter, which provides important linkages between brain regions, is commonly affected by stroke. However, the ability of fMRI to detect white matter activation has only recently been realized and research in this area is in its infancy (Gawryluk et al., 2009; Mazerolle et al., 2010). Lastly, fMRI has been found to be less sensitive in older individuals, like the patients we propose to study (D'Esposito et al., 2003). Therefore, fMRI provides evidence that a brain region is involved in a task. Thus it is complementary to lesion analysis techniques that "...enable us to infer the region is required." (Rorden and Karnath, 2004).

#### 1.3.4.4 Voxel-Based Lesion-Symptom Mapping (VLSM)

A relatively new lesion analysis technique, voxel based lesion-symptom mapping (VLSM) can be used to quantify and compare lesion locations (identified on CT, MRI, or both) with behaviour. Voxels are three-dimensional units of brain volume that are small parts of an imaging slice (Vlaardingerbroek and Boer, 2003). They are typically only a few millimeters cubed on modern MRI scans. VLSM is able to statistically assess a lesion's effect on a given behaviour on

a voxel by voxel basis. This permits the identification of brain regions responsible for a given function without an *a priori* hypothesis (Bates et al., 2003). Recent studies have identified lesion locations associated with hemispatial neglect (Karnath et al., 2011; Mort et al., 2003; Verdon et al., 2010) and language abilities (Bates et al., 2003) post stroke. Analysis at the voxel level permits more precision than previous analyses utilizing ‘lesion overlay’. Also, unlike fMRI studies, which provide a correlational association between brain regions and behaviour (Price et al., 1999), VLSM methods identify regions that play a causal role in a particular domain (Rudrauf et al., 2008b). VLSM has been used to identify cortical (Bates et al., 2003), subcortical (Karnath et al., 2004; Lo et al., 2010b), brainstem (Marx et al., 2008), and cerebellar (Kuper et al., 2011; Schoch et al., 2006) infarcts as well as damage to white matter tracts (Karnath et al., 2009) corresponding to particular behavioural deficits post stroke.

VLSM produces a statistical map that plots the areas associated with poorer behavioural scores. In the analysis, these areas have higher *t*-scores and this is translated into colours on a brain map. To date, no studies have looked at a lesion-symptom relationship for position sense (or any other element of proprioception).

#### **1.4 Rationale**

Proprioception plays a key role in the production and control of movement (Sainburg, 1995; Sarlegna and Sainburg, 2009; Scott, 2002). It is affected in approximately half of all stroke patients (Carey et al., 1996; Reding, 1990), yet our clinical assessments fall short in quantifying these deficits (Carey et al., 1996; Garraway et al., 1976; Lincoln et al., 1991). Since treatment typically follows assessment, substandard measures may fail to detect impairments and thus

appropriate treatment may not be provided, thereby limiting optimal recovery. This study uses a reliable, sensitive, and quantitative robotic assessment of position sense in stroke survivors. Their performance on this assessment is then compared to lesion locations using VLSM to determine anatomical structures responsible for position sense. Identification of brain regions responsible for position sense will further our understanding of sensory deficits resulting from stroke. This is important for predicting sensorimotor recovery and guiding both acute management and therapeutic strategies by rehabilitation professionals.

### **1.5 Aim and Hypothesis**

The aim of this study was to identify brain areas responsible for impaired position sense after stroke. Voxel-based lesion-symptom mapping was used to compare damage in specific voxels to upper limb position sense deficits identified by a robotic assessment.

*Hypothesis: Impaired position sense after stroke will correspond with lesions in the ventral posterior lateral nuclei (VPL) of the thalamus, the posterior limb of the internal capsule, the postcentral gyrus, and the posterior parietal association area.*

## Chapter Two: **Methods**

### **2.1 Research Design**

This cohort design study operated under a larger prospective cohort study (Rehabilitation, Stroke Deficits and Robotic Technology, “RESTART”). This study compares a subset of RESTART data with imaging data for subjects who meet the inclusion and exclusion criteria (below).

#### ***2.1.1 Subjects***

This study sample included 91 subjects with their first clinical presentation of stroke. Individuals were recruited from the Foothills Medical Centre and the Dr. Vernon Fanning Centre in Calgary, Alberta.

#### ***2.1.2 Inclusion/Exclusion Criteria***

Adult subjects aged 18-80 were included in this study if there was a clearly demarcated unilateral ischemic stroke on magnetic resonance imaging (MRI) or computed tomography (CT). Efforts were made to obtain the most homogenous sample possible. In terms of stroke lesion volume, only subjects whose imaging was collected within 10 days of stroke onset were included.

Beyond this time point lesion volume has been shown to decrease dramatically due to resorption of necrotic tissue and resolution of brain edema (Baird et al., 1997; Lansberg et al., 2001; Schwamm et al., 1998).

Hemorrhagic strokes were excluded because these lesions are associated with greater initial stroke severity and poorer neurologic outcomes than ischemic strokes (Barber et al., 2004; Chiu

et al., 2010). Those with cerebellar or brainstem lesions were excluded because they require separate normalization templates (Küper et al., 2011; Schoch et al., 2006) and the methods for combining two templates in one voxel-based lesion analysis have yet to be established.

Individuals were also excluded if they had a history of neurologic disorders, restricted shoulder or elbow range of motion, or upper extremity pain. Notably, stroke severity and/or stroke symptoms were not part of inclusion/exclusion criteria for the study. Subjects provided written informed consent to participate in the study, which was approved by the University of Calgary Conjoint Health Research Ethics Board.

### ***2.1.3 Robotic Assessment***

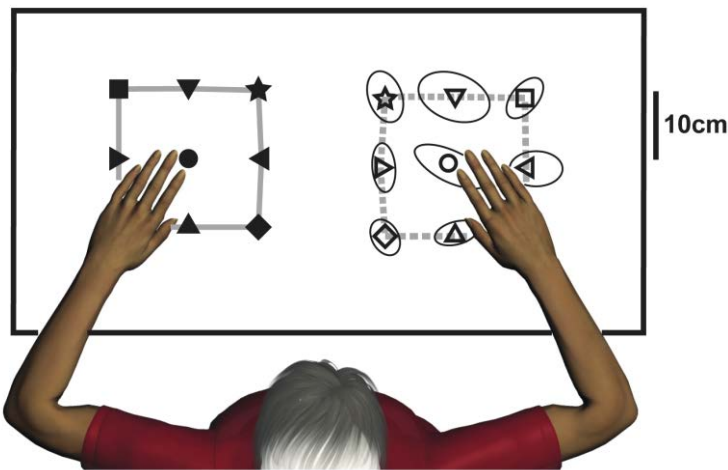
Subjects completed a robotic assessment of position sense using the KINARM exoskeleton robot (BKIN Technologies Ltd, Kingston, Ontario, Canada) within 24 days of stroke onset. This device has been described previously (Coderre et al., 2010; Debert et al., 2012; Dukelow et al., 2010; Scott, 1999). Briefly, subjects were seated comfortably in a wheelchair base with both



arms and hands supported against gravity in forearm troughs (Figure 2). The exoskeleton was adjusted and aligned with the centre of rotation of the subject's elbow and shoulder joints. Alignment of these joints is important to allow relatively friction free movement within the robot. Movement of the upper limbs is constrained to the horizontal plane due to the nature of the device.

**Figure 2 KINARM exoskeleton**

Limb position sense was measured using a robotic position-matching task (Coderre et al., 2010; Debert et al., 2012; Dukelow et al., 2010; Scott and Dukelow, 2011). With vision occluded, the exoskeleton robot moved the stroke-affected arm in a linear path from one target to another using a bell-shaped speed profile. When the robot stopped moving, the subject was asked to move their opposite arm to the mirror location in space (Figure 3). Subjects notified the examiner when they completed each trial and then the examiner triggered the next trial. Target locations were randomized within a block. Each subject completed 6 blocks for a total of 54 trials. In previously



collected control data, the control subjects completed this task twice to permit each arm to be passively moved by the robot while the other mirror matched the position (Herter et al., 2012).

**Figure 3 Position Matching Task**

The KINARM exoskeleton robot moved the subjects left arm to one of 9 spatial locations (filled symbols) in a pseudorandom order. The subject mirror-matched with their right arm with vision occluded. This is representative of typical control data: trial-to-trial variability is represented by ellipses around each point. Each ellipse is one standard deviation, which is less than 5cm in diameter.

The limb position matching task yields 3 parameters that broadly quantify spatial errors made by subjects performing the task and have been shown to be common in individuals after stroke (Dukelow et al., 2010). The *variability* parameter represents trial-to-trial variability of the

matching arm. *Contraction/expansion* represents the subject's interpretation of the overall spatial area they are matching. Finally, *systematic spatial shift* measures the interpretation of workspace location. These 3 parameters result in continuous scores. Exemplar stroke subjects with poor variability, contraction/expansion, and systematic spatial shift scores are presented in Figure 5 alongside a typical control demonstrating good performance. Previous testing of over 200 healthy controls has been used to create normalized data calculations yielding 95% confidence intervals taking age, sex and test-arm (dominant or non-dominant) into consideration (Dukelow et al., 2010; Dukelow et al., 2012; Herter, 2011).

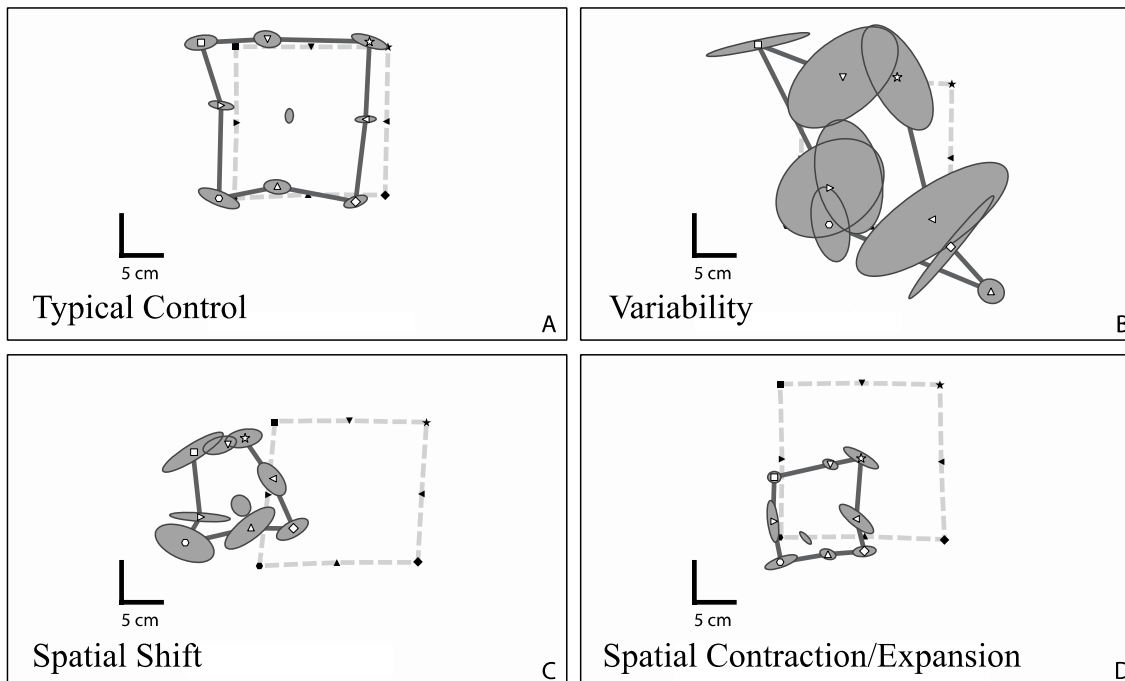
$$A) \text{ var}_{xy} = \sqrt{\text{var}_x^2 + \text{var}_y^2}$$

$$B) \text{ cont/exp}_x = \frac{\text{range}_{x\_active}}{\text{range}_{x\_passive}}$$

$$C) \text{ shift}_{xy} = \sqrt{\text{shift}_x^2 + \text{shift}_y^2}$$

#### Figure 4 Calculations for the 3 Parameters

Calculations for scores for the 3 parameters are determined as follows: A) Variability was calculated by finding the standard deviation of the matching hand's position for each target, then calculating the mean and standard deviations for all target locations in the  $x$  coordinate ( $\text{var}_x$ ),  $y$  coordinate ( $\text{var}_y$ ), and the linear variability for both combined ( $\text{var}_{xy}$ ). B) Spatial contraction/expansion along the  $x$  axis ( $\text{cont/exp}_x$ ) was obtained by finding the difference between the mean  $x$  position for the 3 right and 3 left targets (see Figure 5D) for the matching hand compared to the hand moved by the robot. A similar procedure was conducted to determine  $\text{cont/exp}_y$ . Spatial contraction/expansion along both coordinates was computed by finding the area for the 8 peripheral targets for the matching arm, then normalizing it by the total spatial area spanned by the hand moved by the robot. C) Spatial shift was calculated by finding the mean error between the matching and robot-moved hand, then calculating the means for all target locations. Spatial shifts were obtained for the  $x$ ,  $y$ , and both  $xy$  coordinates. (Dukelow et al., 2010; Herter et al., 2012)



**Figure 5 Position Matching Parameters**

Workspace view of the position matching task parameters. The dashed box represents the arm moved by the robot (passive arm). The data from the matching arm (active arm) has been mirror transformed over the dashed box to quantify discrepancies between the robotically moved arm and the position the individual matched to. A) Typical control data. B) Exemplar stroke subject demonstrating mean trial-to-trial variability beyond typical ranges. Ellipses around the targets represent 1 standard deviation. C) Exemplar subject demonstrating systematic shift of workspace location. D) Exemplar stroke subject demonstrating spatial contraction of workspace area.

A series of clinical assessments were administered by research therapists with stroke rehabilitation experience at the same time point as the robotic task to obtain an overview of the sensory, motor, visuospatial, and functional levels of our subjects. The Thumb Localizing Test of position sense (TLT) is a bedside assessment designed to detect abnormalities in proprioception (Hirayama et al., 1999). The Edinburgh Handedness Inventory is a scale used to determine hand dominance for everyday activities (Oldfield, 1971). The Chedoke-McMaster Stroke Assessment measures physical impairment and disability based on the stages of motor recovery identified by

Twitchell (1951) and Brunnstrom (1970) (Gowland et al., 1993). The Modified Ashworth Scale measures spasticity (Bohannon and Smith, 1987). The Behavioural Inattention Test (BIT) screens for the presence and extent of visual neglect (Wilson et al., 1988). Finally, the Functional Independence Measure assesses physical and cognitive disability in 6 functional domains with the goal of identifying the amount of assistance an individual requires [FIM; (Keith, 1987)]. These data are presented in Table 1.

#### ***2.1.4 MR and CT Acquisition***

All patients had brain lesions due to acute ischemic stroke as demonstrated by MRI (n=73) or CT (n=18). To capture the initial lesion presentation and keep the timing since stroke similar between subjects, only those with imaging collected within 10 days of stroke onset were included in the study. After 10 days post stroke, infarct size decreases due to reabsorption of necrotic tissue and resorption of brain edema (Baird et al., 1997). Robotic assessments were performed as close in time to the imaging assessment as possible.

#### ***2.1.5 Lesion Mapping***

Lesion location was defined using MRICron software [(Rorden et al., 2007): <http://www.mcaslandcenter.sc.edu/mrico/mricron/index.html>] by trained researchers. All lesion maps were then verified and adjusted if necessary by a stroke neurologist, who was blind to the outcome of the robotic assessment. Lesions on CT scans (n=18) were localized with respect to anatomical landmarks and manually transposed onto the normalized MNI template provided in MRICron. Axial slices corresponding to the Montreal Neurological Institute (MNI) z-coordinates -25 to 65 at 5mm increments were used. This methodology has been used previously by other

groups (Karnath et al., 2011; Verdon et al., 2010). For subjects with MRI scans, lesions were marked on each axial slice of the T2 fluid-attenuated inversion-recovery (FLAIR) images in consultation with diffusion-weighted (DWI) sequences. Cost function masks were used for the damaged brain tissue to prevent distortion during the normalization process (Brett et al., 2001). The SPM8 (<http://fil.ion.ucl.ac.uk/spm>) normalization algorithm was used to map the FLAIR scan and lesion shape into stereotaxic space. The normalized MR images were re-sliced to correspond to the MNI coordinates used for the CT's. To group all lesions during final calculations, left hemispheric lesion maps were mirrored across the midsagittal axis using the standard procedure in MRICron. This methodology is typical of lesion analyses investigating motor function after stroke (Lo et al., 2010b; Zhu et al., 2010). The resulting lesion images were used for the subsequent voxel-based statistical analysis using MRICron.

### ***2.1.6 Voxel-based Lesion-Symptom Mapping (VLSM) Analysis***

Voxel-based lesion-symptom mapping (VLSM) was used to determine the anatomical correlates of the three parameters of the position-matching task (variability, systematic spatial shift, and contraction/expansion). Each parameter provides a continuous score. With VLSM, *t*-tests are run at each voxel, comparing performance in subjects with and without a lesion involving that voxel. Thus, for any particular voxel, a *t*-test is performed with lesion status as the independent variable (lesioned or not) and behavioural performance (in this case, position-matching) as the dependent variable. In this study, *t*-tests were confined to those voxels that were damaged in at least 5% of the sample. Though no criterion exist for determining this threshold, 5% has been used in recent VLSM studies with sample sizes similar to ours (Baldo et al., 2013; Gauthier et al., 2009). Even with such thresholds employed, VLSM analysis conducts thousands of *t*-tests, resulting in the

need to control for multiple comparisons. The False Discovery Rate (FDR) control for multiple comparisons has been advocated as an alternative to the Bonferroni method in voxel-based lesion analysis (Rorden et al., 2007). The FDR controls for the expected proportion of false positives among all voxels above a specific threshold (such as 0.05) (Genovese et al., 2002). The FDR correction has been used in numerous VLSM studies (Committeri et al., 2007; Glascher et al., 2010; Karnath et al., 2011; Lo et al., 2010b). As such, the present study used the FDR to control for multiple comparisons.

### ***2.1.7 Overlap Map***

Using MRICron, an overlap map was generated to identify all lesioned voxels in our sample (prior to statistical testing) and demonstrate the most common areas of damage. This map was not thresholded, therefore, even single voxels appear on the map.

### ***2.1.8 Region of Interest Analysis***

Regions of interest (ROI) were drawn for the insula, PLIC, VPL of the thalamus, postcentral gyrus, and the posterior parietal association area (superior parietal lobule, medial intraparietal sulcus, posterior paracentral lobule, and precuneus) using MRICron. The Julich probabilistic cytoarchitectonic atlas (Bürgel et al., 2006) (for the PLIC) and the Brodmann's areas template (for the posterior parietal association area) included with MRICron were used to guide the creation of the ROIs. The normalized lesion images were co-registered to the 1x1x1mm voxel ROIs with SPM8 to provide equitable slices and complete regional representation. The lesion images from the entire sample were then compared to each ROI using the non-parametric mapping package (NPM) that is included with MRICron. Thus, the ROI analysis provided

another means of testing our hypothesis. The ROI analysis was used to address 4 questions: 1) does ROI damage predict performance on individual parameters of the position matching assessment? 2) Does ROI damage predict failure of the position matching task? 3) Is the number of ROI's damaged predictive of position matching task failure? 4) Do combinations of ROI's damaged predict failure of the position matching task?

For the ROI analysis, individual subject performance was determined using pass/fail cut-off scores, for each parameter. These cut-off scores were based on normalized data calculations for each subject based on age, sex and handedness that were created previously for the position match task (Dukelow et al., 2012; Herter, 2011). A subject's performance on a parameter was considered a "fail" if it fell outside the parameter's normative reference range, defined as the 95% confidence interval based on control performance taking age, sex, and test-arm (dominant or non-dominant) into consideration. In other words, the confidence interval for each parameter is customized to the subject's age, sex, and whether their affected arm is their dominant or non-dominant side. For variability and shift, hand dominance is factored in, therefore the slope and intercept values for the corresponding (dominant/non dominant) upper extremity are used. For contraction/expansion, p50 represents a perfect match of workspace area, while values below p2.5 or above p97.5 represent abnormally contracted or expanded workspace area respectively.

The equations for the normalized reference range for the 3 parameters are as follows:

Variability xy                      Boundary = exp (slope \* age + bias + percentile)

Shift xy                                Boundary = (slope \* age + bias + percentile)<sup>2</sup>

Contraction/Expansion      Boundary = (age \* slope) + bias + percentile)

$$p2.5 = (\text{age} * \text{slope}) + \text{bias} - 0.362$$

$$p97.5 = (\text{age} * \text{slope}) + \text{bias} + 0.425$$

$$p50 = (\text{age} * \text{slope}) + \text{bias} - 0.009$$

## Chapter Three: **Results**

### **3.1 Subjects**

This study compared the clinical imaging and robotic position matching data of 91 subjects to investigate the relationship between lesion location and position matching deficits after stroke. The demographic and clinical features of these subjects are presented in Table 1. Although more subjects had right brain lesions (n=51) than left (n=40), these two groups exhibited relatively similar demographic, clinical, and timing (between stroke/imaging/robotic assessment) profiles. One notable exception is that the number of individuals with visuospatial neglect was higher in the group with right brain (n=18) versus left brain (n=4) damage. Descriptive statistics for group performance on the 3 position match parameters are presented in Table 2.

	Stroke Subjects		Control Subjects
	(R) Brain Lesion (L) Arm affected n=51	(L) Brain Lesion (R) Arm affected n=40	(Collected Previously)**** n=209
Age in years (range)	65 (25-86)	62 (31-89)	48 (18-90)
Sex	11F, 40 M	19F, 21M	113F, 96M
Dominant Hand	47R, 2L, 2A	36R, 3L, 1A	188R, 12L, 9A
Vascular Territory(ies)			
ACA	1	2	-
MCA	39	32	-
PCA	6	5	-
ACA & MCA	2	0	-
MCA & PCA	1	0	-
ACA & PCA& MCA	1	1	-
ANT CH	1	0	-
Neglect*	18	4	-
FIM**	103 (43-126)	106 (65-126)	-
TLT [0,1,2,3]***	[25, 18, 4, 4]	[28, 7, 2, 2]	-
CMSA [1,2,3,4,5,6,7]: Affected Arm Less Affected Arm	[4,2,3,2,13,8,19] [0,0,0,0,3,11,26]	[3,0,3,2,6,9,17] [0,0,0,0,0,1,50]	-
MAS [0,1,1+,2,3,4] Affected Arm Less Affected Arm	[37,7,4,3,0,0] [50,1,0,0,0,0]	[37,2,1,0,0,0] [40,0,0,0,0,0]	-
Days Between Stroke and Imaging	1 (median) (0-7)	1 (median) (0-10)	-
Days Between Stroke and Assessment	8 (median) (2-24)	8 (median) (2-24)	-

**Table 1. Demographics**

Abbreviations: F/M, female, male; R/L/A, right, left, ambidextrous; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; ANT CH, anterior choroidal artery; FIM, Functional Independence Measure; TLT, Thumb Localizing Test; CMSA, Chedoke McMaster Stroke Assessment; MAS, Modified Ashworth Scale.

Age and FIM are indicated as the median followed by the range within parentheses.

\* Neglect was determined by a score less than 130 on the Behavioural Inattention Test

\*\*FIM score unavailable for 2 left affected subjects and 1 right affected subject. These subjects were not included in the calculation of the median

\*\*\* Score unavailable for 1 (right side affected) subject

\*\*\*\* (Dukelow et al., 2012; Herter et al., 2012)

- Not applicable for control subjects

	Stroke Subjects n=91	Healthy Controls n=209
Variability Mean (SD)	7.49 (4.66)	3.50 (0.90)
Contraction/Expansion Mean (SD)	1.03 (0.71)	0.83 (0.21)
Spatial Shift (SD)	7.2 (6.69)	4.22 (2.31)
Age in years (median)	64	48

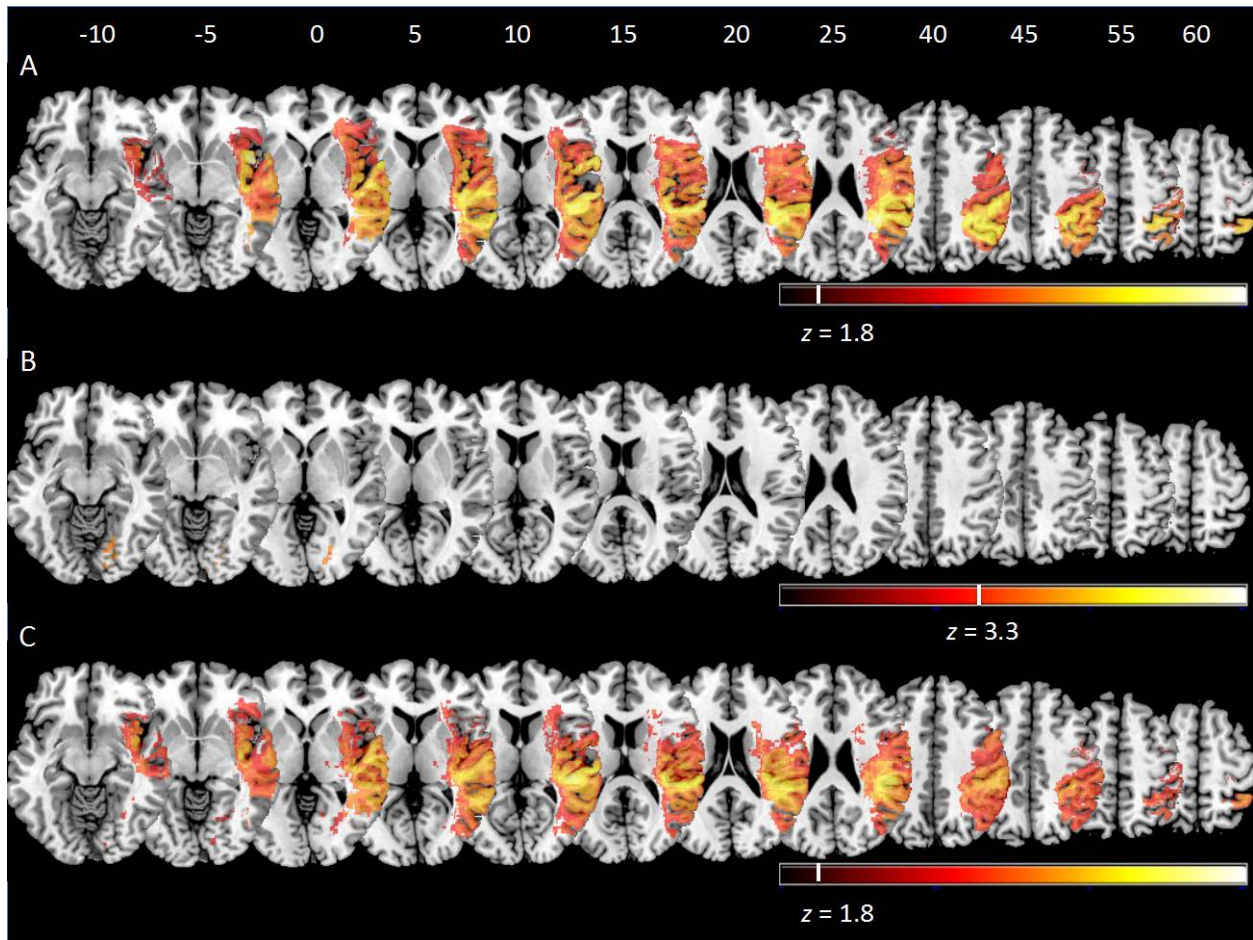
**Table 2 Means and standard deviations per parameter**

Mean scores and standard deviations (SD) for each of the 3 position match parameters collected from this study's sample and from previously collected control subjects reported in (Dukelow et al., 2012; Herter et al., 2012). Data were asymmetrically distributed in the positive direction. Means are presented here to provide a comparison of the two groups. Units are in centimeters.

### **3.2 Voxel-based Lesion-Symptom Mapping (VLSM) Findings**

#### **3.2.1.1 VLSM Map: Variability Parameter**

The statistical map comparing lesion location and continuous scores for the variability parameter (the trial-to-trial consistency of the matching arm) of the position matching task is shown in Figure 6a. Only voxels that survived the False Discovery Rate (FDR) correction ( $z = 1.81$ ,  $P < 0.05$ ) are presented. The colour range represents  $z$ -scores from least significant (dark red) to most significant (white). Highly variable (poor) performance on the position matching task is shown on the map in yellow. Thus damage to the postcentral gyrus, posterior parietal association area ([PPAA], as defined in section 1.2.1.4), insula, middle temporal gyrus, and superior temporal gyrus, are most associated with poor performance on the variability parameter of the position matching task.



**Figure 6 VLSM maps**

Statistical voxel-based lesion-symptom mapping (VLSM) analyses for the 3 parameters of the KINARM position-matching task. The continuous scores for each parameter were compared to voxel damage using the  $t$ -test statistic (presented as  $z$ -scores). Only voxels significant at  $P < 0.05$  (false discovery rate corrected) are presented. The colour range indicates  $t$ -test values from VLSM analysis, from black (non-significant) to white (maximum significance). A. Variability parameter. B. Spatial shift parameter. C. Spatial contraction/expansion parameter.

### 3.2.1.2 VLSM Map: Systematic Spatial Shift Parameter

The systematic shift parameter represents the subjects' interpretation of their workspace location. Shown in Figure 6b, the VLSM map for systematic shift only displays voxels that survived the FDR ( $z = 3.3$ ,  $P < 0.05$ ). The lingual gyrus was only brain area where damage was highly related to poor scores on the shift parameter of the position matching task.

### 3.2.1.3 VLSM Map: Spatial Contraction/Expansion

The VLSM map for the contraction/expansion parameter is shown in Figure 6c. This parameter represents the subjects' interpretation of the area/range of the workspace. Presented are only voxels that survived the FDR ( $z = 1.85$ ,  $P < 0.05$ ), poor contraction/expansion scores were associated with damage to the insular cortex as well as the middle temporal, superior temporal and postcentral gyri.

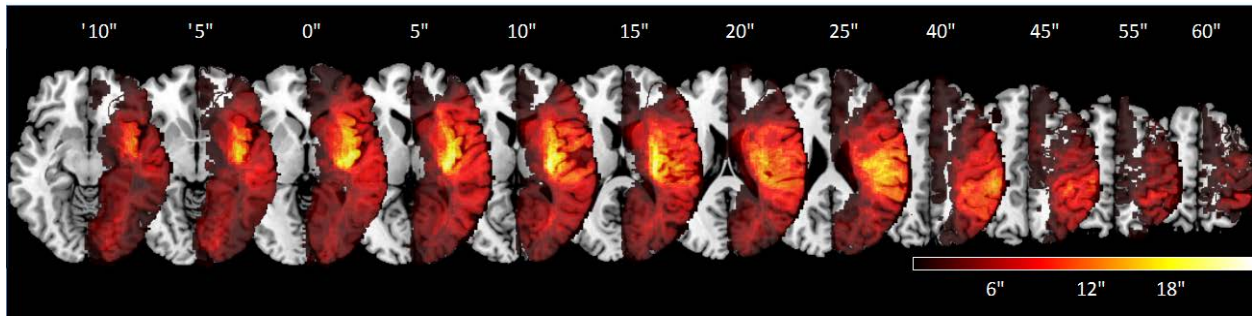
### 3.2.1.4 VLSM Maps: Comparisons

A visual comparison of the 3 VLSM maps for each parameter of the position matching task reveals that each map contains results unique to that parameter. The shift map was strikingly different than the other two maps as the lingual gyrus was the only area to demonstrate a relationship between damage and poor spatial shift scores. The variability and contraction/expansion maps are very similar, with one key difference. The main difference between the two maps is that the inferior frontal gyrus is associated with poor variability scores but not with poor spatial contraction/expansion scores. In terms of similarity, both parameters involve the somatosensory (postcentral gyrus) and the posterior parietal cortices and associated white matter in addition to the insula, middle and superior temporal gyri. The  $z$ -values were

almost identical for variability and contraction/expansion despite behavioural differences between these two groups (section 3.3.2). Overall, the differences among the maps of the 3 parameters of the position matching task may indicate that each parameter represents related, but slightly different features involved in the overall construct of sense of limb position.

#### 3.2.1.5 Overlap Map

A simple overlap of the 91 brain lesions from our sample is presented in Figure 7. Like the VLSM maps in Figure 6, the overlap map is in the same standard stereotaxic space as the Montreal Neurologic Institute [MNI (Holmes et al., 1996)] template brain, which permits a direct comparison to be made. It is clear that the maximal area of overlap (Figure 7) is in the insular region and the superior corona radiata. While these two brain regions appear in the variability and contraction/expansion parameter VLSM maps, simple overlap is not predictive of performance on the position matching task. This is evidenced by numerous areas associated with poor position match scores on the VLSM maps that are not distinct on the overlap map such as the postcentral gyrus, posterior parietal association area, thalamus, pre-central gyrus, inferior frontal gyrus, as well as the superior and middle temporal gyri. Thus the disparity between the two types of maps indicates that the brain regions associated with poor position match scores on the VLSM maps is not due to concentration of damage.



**Figure 7** Overlap Map of brain lesions of all 91 subjects

Overlap map of all 91 subjects. Left hemisphere lesions have been flipped into the right hemisphere. Maximal overlap is indicated by the colour white and black represents voxels damaged in only one subject.

### 3.3 Region of Interest Analysis

#### 3.3.1 ROI Analysis Provides Verification of VLSM Analysis

ROI's were drawn for the VPL of the thalamus, the PLIC, insula, postcentral gyrus, and the PPAA. This analysis provided an efficient means of determining if these areas were damaged for each individual subject. A cut-off score was used to determine if subjects failed a given parameter. Table 3 provides an overview of subject characteristics according to pass/fail performance on the 3 parameters. Overall, the ROI analysis results were similar to those of the VLSM analysis. As seen in Table 4, damage to each of the selected ROI's was associated with parameter failure. Further, the trend seen in the spatial shift VLSM maps may be partially explained by the ROI analysis which revealed that fewer subjects fail that parameter in comparison to the other two parameters.

		Age (median) in years	Sex (F/M)	FIM (mean)	Subjects with Neglect	Vascular territory M/P/A/AC/MP/MA/MPA
Variability	Pass	64	18/24	108.7	2	34/4/2/1/0/0/1
	Fail	65	12/37	93.4	20	37/7/1/0/2/1/1
Contraction/ Expansion	Pass	64	17/30	109.5	3	38/4/3/1/0/0/1
	Fail	64.5	13/31	93.0	18	33/7/0/0/2/1/1
Spatial Shift	Pass	64	22/41	103.7	11	50/8/2/1/0/1/1
	Fail	64.5	8/20	95.9	12	21/3/1/0/2/0/1

**Table 3 Characteristics of subjects who passed and failed each parameter**

Abbreviations: F/M, female, male; FIM, functional independence measure; M, middle cerebral artery; P, posterior cerebral artery; A, anterior cerebral artery; AC anterior choroidal artery; MP, middle & posterior cerebral arteries; MA, middle and anterior cerebral arteries; MPA, middle, posterior and anterior cerebral arteries. Neglect was determined by a score of less than 130 on the Behavioural Inattention Test. Pass/Fail scores were based on a previously-determined normative reference range (95% confidence interval) taking into account a subjects age, sex, and whether the stroke-affected arm was their dominant or non-dominant arm (Herter, 2011; Herter et al., 2012). The pass/fail cut-off scores were only used for the ROI analysis.

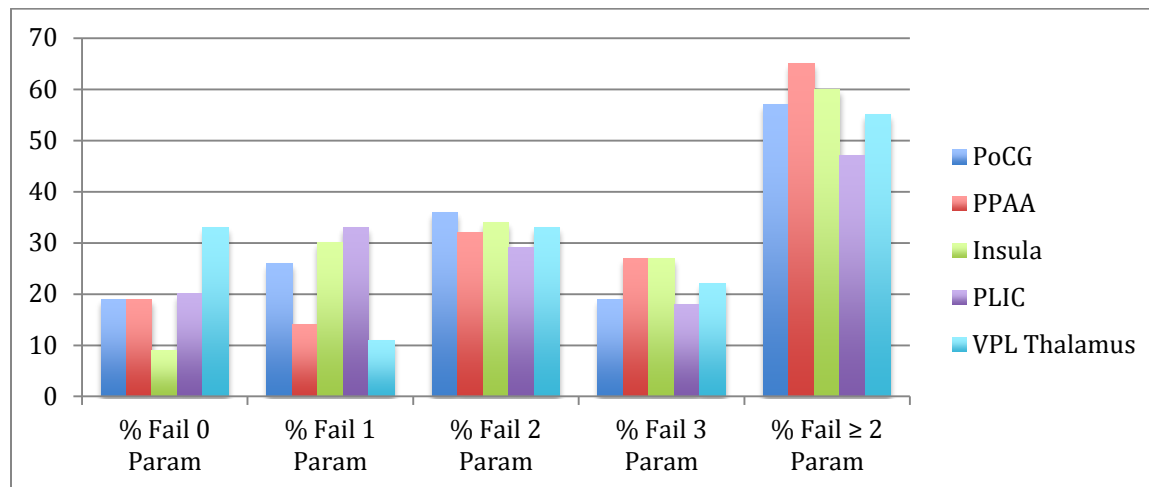
### ***3.3.2 Does ROI Damage Predict Performance on Individual Parameters?***

A similar number of subjects had damage in each ROI, with the exception of the VPL of the thalamus – this area was only damaged in 9 subjects (10% of the sample), as shown in Table 4. However, just over half of those subjects failed 2 or more parameters, demonstrating that this ROI is strongly associated with poor performance on the position matching task. This proportion is similar to the others (Figure 8). Damage to each ROI resulted in a 47% to 65% likelihood of failing the position matching task. Thus, it does not appear that subjects with damage in any one of the ROI's have a predilection to fail one parameter over another.

	Postcentral Gyrus	PPAA	Insula	PLIC	VPL Thalamus
Subjects with damage in ROI (% of sample)	42 (46%)	34 (37%)	44 (48%)	45 (49%)	9 (10%)
Variability	27	25	30	27	4
Systematic Shift	13	11	18	15	2
Contraction/ Expansion	25	23	29	23	5

**Table 4. ROI damage associated with poor scores in the 3 position match parameters.**

Relationships between ROI's and individual parameters failed. For each ROI, the number of subjects with damage in that ROI is noted. The bottom 3 rows indicate which parameters these subjects failed. Total sample size is 91. Several subjects failed more than one parameter. Very few subjects had damage to the VPL of the thalamus; otherwise proportionate damage across ROI's was similar. Abbreviations: PPAA, posterior parietal association area; PLIC, posterior limb internal capsule; VPL, ventral posterolateral nucleus of thalamus.



**Figure 8 ROI and parameter comparisons**

Percentage of subjects with damage to a given ROI who fail 0, 1, 2, 3, or 2 or more position matching parameters. Failure of an individual parameter was determined by a cut-off score. Failure of 2 or more parameters is considered task failure. Performance was relatively proportionate across the ROI's for those failing 2 or more parameters. Abbreviations: PoCG, postcentral gyrus; PPAA, posterior parietal association area; PLIC, posterior limb internal capsule; VPL, ventral posterolateral nucleus of thalamus.

	Number of subjects with region combination	Postcentral Gyrus	PPAA	Insula	PLIC	VPL of Thalamus
<b>1 Region</b>	3		x			
	2			x		
	2				x	
<b>2 Regions</b>	3	x	x			
	3	x		x		
	4			x	x	
	1				x	x
<b>3 Regions</b>	6	x	x	x		
	3	x		x	x	
	2		x		x	x
	1			x	x	x
<b>4 Regions</b>	8	x	x	x	x	
	1	x		x	x	x

**Table 5. ROI combinations**

Combinations of ROI's damaged in subjects who failed two or more parameters of the position matching task. Several subjects had damage to more than one ROI. Abbreviations: PPAA, posterior parietal association area; PLIC, posterior limb internal capsule; VPL, ventral posterolateral nucleus of thalamus.

### ***3.3.3 Does Specific ROI Damage Predict Failure on the Position Matching Task?***

A subject who fails 2 or more parameters fails the position-matching task and is considered to have poor position sense (Debert et al., 2012). Figure 8 presents the percentage of subjects with damage to a given ROI who fail the position-matching task: 50% had damage to the VPL of the thalamus; 47% to the PLIC, 61% to the insula; 55% to the PoCG; and 65% to the PPAA.

Interestingly, 20% of subjects with damage in the PoCG, PPA or PLIC passed all three parameters. To summarize, while damage to any of the ROIs was associated with approximately a 50% chance of failing the position-match task, no one ROI was more associated with task failure than the others.

### ***3.3.4 Is The Number of ROIs Damaged Important for Position Sense?***

The vast majority of subjects who failed the position-matching task had damage to more than one ROI. This raised the question: did the number of ROIs damaged have a bearing on the outcome? For example, if 3 ROI's were damaged, did the chances of having poor position sense increase? Table 5 provides a breakdown of the number and combination of ROI's observed in subjects who failed the position matching task. The number of ROIs damaged did not predict poor position sense – the odds of failing the task were fairly equal despite the number or ROIs damaged.

### ***3.3.5 Do Combinations of ROIs Damaged Predict Position Sense?***

It would be reasonable to suspect a pattern among ROIs - that damage to a particular combination of ROIs was more likely to produce poor position-matching scores than a different combination. However, when 2 and 3 ROIs were damaged, 4 combinations of ROIs presented themselves – none dominant over the others (Table 5). When 4 ROIs were damaged, only 2 combinations existed. This may be more indicative of vascular patterns of a large MCA stroke, however, than an interaction among ROIs.

## Chapter Four: **Discussion**

The aim of this study was to identify brain areas responsible for impaired position sense after stroke. We used voxel-based lesion-symptom mapping to achieve this goal. VLSM is a novel method that compares behavioural performance with damage (or not) at each voxel across the sample. To overcome the measurement issues typically associated with clinical position sense assessment, we quantified position sense using a sensitive and reliable robotic assessment that was previously established (Dukelow et al., 2010). Our VLSM analysis produced statistical maps to identify areas that, when damaged, were associated with poor position sense as identified by the robotic task. The maps we produced were for each of the 3 parameters of the position match task. The 3 parameters produced distinctly different maps, possibly indicating that each parameter represents related but slightly different features involved in the overall construct of limb position sense. Further, we conducted a Region of Interest (ROI) analysis to provide another means of testing our hypothesis. The ROI analysis supported the VLSM findings and afforded a means of answering additional questions of our sample. The outcomes of this study provide fodder for several points of discussion.

### **4.1 Methodologic Considerations**

#### ***4.1.1 MRI's Include a Diffusion-Weighted sequence, CT's Do Not***

In order to achieve the sample size required to produce stable VLSM maps, we included subjects who had either MR or CT scans. This is common practice for VLSM studies investigating the relationship between brain regions and behaviour after stroke (Karnath et al., 2011; Verdon et al.,

2010). An important advantage that MR sequences have over CT scans is that they (in our sample) include diffusion-weighted images (DWI). The DWI sequence is sensitive to shifts of water between extra and intra-cellular spaces and is able to detect ischemic cell death early after stroke (Ricci et al., 1999). We used the DWI sequence to verify the presence of an acute lesion. Two subjects (n=16) with CT also had a diffusion-weighted sequence because a MRI was initiated but was stopped at the subject's request prior to completion of all sequences.

#### ***4.1.2 Creation of an ROI for the VPL of the Thalamus***

The ROI used in the present study for the VPL of the thalamus has very little overlap with the majority of thalamic damage that appears on the VLSM map. Various factors may account for this discrepancy. First, we created the thalamic VPL ROI using a popular MRI atlas (Oishi et al., 2010) as a guide. In this text, thalamus parcellation was based solely on the orientation information in diffusion tensor imaging of 20 normal subjects. Thus, issues inherent in the tractography technique or sampling may have resulted in a slightly different VPL nucleus location than that of our sample. Secondly, when drawing the ROI we were reliant on visual transference of information from the atlas to the MRI template. Thus, an operator error or slight anatomical template difference between the MRI in the atlas and the MRICron template could have resulted in an incorrect placement of the ROI. Thirdly, the possibility exists that the data on our VLSM map is in a nucleus adjacent to the VPL. Finally, it is possible that the normalization transform distorted the location of the VLSM data slightly. However, this is unlikely since a rigorous visual check of the normalized subcortical structures at the level of the basal ganglia revealed satisfactory normalization.

## **4.2 Brain Regions responsible for position sense**

### ***4.2.1 Results Congruent With Hypothesis***

#### 4.2.1.1 VPL of the Thalamus

The VPL of the thalamus was only associated with poor spatial contraction/expansion scores.

Very few subjects (n=9) in our sample had damage to the VPL of the thalamus. This may be due to 2 factors. First, the thalamus is perfused by the PCA, however the incidence of PCA strokes compared to MCA is very low (Arboix et al., 2011). Secondly, our sample excluded subjects with brainstem involvement. Since deep PCA artery branches perfuse the brainstem in addition to the thalamus (Schmahmann, 2003), we may have inadvertently limited the number of subjects with thalamic strokes for our study.

Historically, the thalamus (in this case, the VPL nucleus of the thalamus) was considered an important relay of sensory information. More specifically, the core of the VPL nucleus receives tactile information while the shell receives proprioceptive inputs (Weber et al., 2012). Damage to these areas is believed to result in sensory impairments because of transmission disruption.

However, recent findings may expand the role of the thalamus. In mice, sensory information is passed back to the thalamus en route to other cortical areas, indicating that the thalamus plays a role in further processing of this information (Theyel et al., 2010). If this is true in humans, it may help explain why thalamic damage has been linked to body orientation dysfunction in some studies (Karnath, 2007) but not others (Baier et al., 2012; Ticini et al., 2009). In our study, damage to the VPL of the thalamus, resulted in poor scores on the spatial contraction/expansion parameter. It is plausible that thalamic damage impacted the processing of the multiple sensory inputs that result in calculation of workspace area (spatial contraction/expansion with our task),

either via local processing or transmission interruption between the thalamus and sensory areas.

As noted above, our inclusion criteria may have limited the number of subjects with thalamic damage. Therefore, it is possible that a sample with an increased proportion of thalamic damage may show an association with other position match task parameters as well.

#### 4.2.1.2 Posterior Limb of the Internal Capsule

Damage to the posterior limb of the internal capsule (PLIC) was associated with poor variability and spatial contraction/expansion scores. All voxels appearing on the maps were in the posterior aspect of the PLIC (extremely posterior for variability), which is consistent with findings in early case studies (Groothuis et al., 1977) and recent probabilistic maps that the posterior aspect of the PLIC consists of connections between the thalamus and sensory cortices (Behrens et al., 2003). Corticospinal tract (CST) axons are also found in this region of the PLIC. Impaired grip (strength and stability) after human stroke has been attributed to damage in the posterior PLIC in several studies (Schulz et al., 2012; Wenzelburger et al., 2005). This impairment was attributed to interference of CST motor fibre transmission. Interestingly, the CST also contains connections between the primary somatosensory cortex and the dorsal horn, raising speculation that this tract is involved in the descending control of sensory inputs (Lemon and Griffiths, 2005). Though our VLSM maps cannot determine if the PLIC damage is specific to afferent or efferent fibres, they confirm that this region is involved in processing position sense information.

#### 4.2.1.3 Postcentral Gyrus and Posterior Parietal Association Area

Damage to the postcentral gyrus and the posterior parietal association area was strongly associated with poor variability and spatial contraction/expansion scores. The postcentral gyrus

contains Brodmann's areas 3a, 3b, 2 and 1 and is typically referred to as the primary somatosensory cortex (Amaral, 2013). These areas appear to receive differing proportions of sensory inputs. This information is processed in a progressively unimodal to multimodal fashion, with some of the information projected to areas in the posterior parietal association area (PPAA). The PPAA has extensive cortical connections and integrates multiple sensory inputs to process world referenced spatial coordinates used to guide reach, grasp, and skilled hand movements (Kandell, 2013) (Andersen and Cui, 2009; Baumann et al., 2009; Kalaska et al., 1983; Lacquaniti et al., 1995; Sakata et al., 1997; Scott et al., 1997). Lesions to the above areas result in perceptual impairments relating to the modalities they process. In our study, VLSM maps revealed that damage to the postcentral gyrus and the posterior association area was related to poor scores for the variability and spatial contraction/expansion tasks.

#### ***4.2.2 Results beyond the hypothesis***

##### ***4.2.2.1 Lingual Gyrus***

Damage to the lingual gyrus was related to poor spatial shift and poor spatial contraction/expansion scores. In fact, this was the only brain region that appeared on the spatial shift map. This parameter had the lowest rate/incidence of failure (n=28 failed, approximately 1/3 of the sample) and this may be reflected in the small region of damage on this map.

Investigation into a possible relationship between the lingual gyrus and spatial position matching revealed that this region belongs to a cortical network involved in short term spatial memory (Sulpizio et al., 2013). This study used vision where ours did not. However, perhaps the visual cortex is involved in processing spatial locations required to reproduce workspace location (spatial shift) and workspace area (spatial contraction/expansion).

#### 4.2.2.2 Inferior Frontal Gyrus

It is of interest that the VLSM map for the variability parameter of the position match task demonstrated a connection between interpretation of sensory information and the inferior frontal gyrus. There is a vast amount of literature on the relationship between the posterior parietal cortex [which includes the posterior parietal association area as well as the inferior parietal lobule (Andersen and Cui, 2009; Gardner and Johnson, 2013)] and the prefrontal cortex [which includes the inferior frontal gyrus (Petrides, 2005)]. Briefly, it is a popular view that different dorsal and ventral pathways exist for processing each sensory modality (visual, auditory or somatosensory) (Olson and Colby, 2013). As discussed above, individual functional areas exist within the posterior parietal cortex such as those involved in processing spatial information for arm movement and reach [area 5, (Lacquaniti et al., 1995; Scott et al., 1997)] as well as grasping [anterior intraparietal area; (Baumann et al., 2009; Sakata et al., 1997)]. The posterior parietal cortex is also important for spatial attention (Andersen and Buneo, 2002). Through association pathways, the posterior parietal cortex communicates with frontal areas such as the prefrontal cortex (Vincent et al., 2008). This region plays an important role in working memory and modulation of association areas towards task-relevant information (Gruber and Goschke, 2004; Petrides, 2005). Thus, the prefronto-parietal network is anatomically positioned to integrate sensory information to initiate and guide movement. Since the position match task requires an individual to feel the position of their robot-moved arm, attend to this information, move their other arm to mirror-match the position, and then decide if the position matches, it is fitting that prefronto-parietal network would be important for success in the variability parameter.

#### 4.2.2.3 The Insula

Damage to the insula was strongly associated with poor variability and, to a slightly lesser extent, spatial contraction/expansion scores on the position match task. As discussed briefly in the introduction (section 1.2.1.4), the insula appears to play a role in integration of polymodal sensory information. In regards to somatosensory information, the insula receives inputs from the anterior parietal lobe. This connection is believed to be involved with higher-order bodily awareness such as feelings of ownership of limbs (Karnath et al., 2005), knowing that one was responsible for their movement (Farrer and Frith, 2002), and subjective feelings of one's movement (Craig et al., 2009). Our results indicate that the insula is involved when judging whether arm positions are matched or not.

#### 4.2.2.4 Superior and Middle Temporal Gyri

Damage to the superior and middle temporal gyri were strongly associated with poor scores on the variability and spatial contraction/expansion parameters. Though these gyri are involved in numerous functions such as language processing and memory, this discussion will focus on aspects pertinent to the processing of somatosensory information. According to human and non-human primate evidence, the superior temporal gyrus has extensive connections with the occipital, insular, and parietal lobes via the superior longitudinal fasciculus, which is part of the fronto-parietal network (Makris et al., 2005; Makris et al., 2013; Petrides and Pandya, 1988). Functional MRI studies have found that this region is involved in voluntary visual orienting (Himmelbach et al., 2006) and visuospatial attention (Makris et al., 2013). Damage to the superior and middle temporal gyri has been associated with spatial neglect (Chechlacz et al., 2013; Karnath, 2001; Karnath et al., 2004; Karnath et al., 2011; Mort et al., 2003; Verdon et al.,

2010). Our sample included 22 individuals with neglect (18 left; 4 right side neglect). Further VLSM analysis as to the impact these individuals have on our sample is beyond the scope of this thesis, but would be of interest. To conclude, damage to the superior and middle gyri demonstrated an association with poor variability and spatial contraction/expansion scores. Though our position match task did not utilize vision, the involvement of these brain regions may lead to two possibilities: either these areas may be responsible for developing one's own sense of body perception/spatial awareness, or the subjects with neglect may have impacted the VLSM analysis.

#### ***4.2.3 Section Summary***

Overall, our analysis revealed that our hypothesized areas (the thalamus, PLIC, postcentral gyrus and the PPAA) in addition to areas beyond our hypothesis (lingual gyrus, inferior frontal gyrus, insula, and the superior and middle temporal gyri) are involved in the processing of information required for success on parameters of the position match task. Damage to differing brain regions was associated with poor performance for individual parameters. This may indicate that each parameter represents features involved in the overall construct of sense of limb position. As such, position sense appears to be a multi-dimensional construct, processed via a distributed network of brain regions. It is not surprising, then, that this percept is challenging to assess. Sensitive and reliable assessments are required to guide treatment and research into the role of proprioception in motor recovery and improved function after a stroke.

## **4.3 Clinical Implications**

### ***4.3.1 Behavioural Assessments Are Essential for Identification of Position Sense Deficits***

In this study, structural imaging alone was not able to account for all behavioural deficits identified using the highly sensitive robotic position sense assessment. The Region of Interest (ROI) analysis revealed that damage to a given region was associated with poor position match task performance approximately 50-60% of the time, resulting in 40-60% of subjects with damage to the ROIs that did not share these deficits. Thus, reliable and sensitive behavioural measures are required in addition to imaging when identifying damaged brain regions and position sense deficits. The importance of targeted, specific behavioural assessment has also been identified in VLSM studies investigating the neural correlates of hemispatial neglect after stroke. While several VLSM studies have identified a wide range of brain regions associated with hemispatial neglect on the basis of varied general clinical assessments, Verdon et al (2010) identified specific behavioural neglect profiles and revealed neural correlates for each. They postulated that specific behavioural assessments provide a better understanding of the components of neglect. The same is likely true for proprioception. Quality position sense assessments are an essential adjunct to imaging for the identification of proprioceptive deficits after stroke.

### ***4.3.2 Assessing Proprioception – 3 Behavioural Manifestations of Position Sense Deficits***

The robotic position sense task used in this study demonstrated that stroke subjects differentially made up to 3 types of errors and VLSM analysis revealed that each error type (parameter) was associated with damage to different brain areas. Thus position sense deficits resulted in 3 different behavioural manifestations; misinterpretation of limb position, workspace area, and

location. These qualities are not represented in clinical proprioceptive assessments. This is not surprising, given that they have been found to lack sensitivity (Lincoln et al., 1991). However, at the root of any solution is the recognition of a problem. Two recent systematic reviews have identified the need for accessible, quantitative, valid, reliable, and sensitive clinical assessments of sensation after stroke (Connell and Tyson, 2012; Schabrun and Hillier, 2009). Similarly, it is important that clinicians appreciate both the shortcomings of our assessment tools as well as the value that well-honed observational skills can contribute to assessment. Ideally reciprocal communication (Group et al., 2009) between clinical and research communities will drive improvements in the reliability, sensitivity, and behavioural features of proprioceptive assessments.

### ***4.3.3 Assessing Proprioception: Inclusion of Both Static and Movement Sense***

#### ***4.3.3.1 Clinical assessment of static position sense versus dynamic movement sense***

When assessing “proprioception” clinicians may use one of a few tests, but they are unlikely to assess both the static and dynamic components. To test static joint position sense, a proximal joint (Lincoln et al., 1991), finger (Bickley and Szilagyi, 2007), or toe (Bickley and Szilagyi, 2007) is passively placed in a position and the client is asked to replicate or describe that position. Similarly, to test for movement sense, a finger or great toe is moved up or down and the client is asked to describe the movement direction (Bentzel, 2007). Some clinicians may also use the thumb localizing test (Hirayama et al., 1999) in which the affected arm is positioned and, without using vision, the client locates their thumb with the contralateral hand. Although clinicians appreciate the difference between position sense (which may also be referred to as sense of static joint position) and kinaesthesia (perception of limb movement), most

neurorehabilitation assessments only include 1 measure of “proprioception.” This may involve either a static or dynamic test in the absence of vision. However, recent evidence indicates that our perception of active and passive proprioceptive information differs. Studies on healthy human subjects have consistently found reduced errors when active movement is used to establish a static reference position as opposed to being moved passively into position (Erickson and Karduna, 2012; Goble, 2010; Laufer et al., 2001). Given that static position and dynamic movement senses are processed differently in the periphery (section 1.2.1.3) and appear to result in dissimilar performance in healthy subjects, it may be beneficial for clinical stroke assessments to include both of these subcomponents of proprioception.

#### ***4.3.4 Consideration of Sensory Function When Predicting Stroke Recovery***

Our results revealed several brain regions involved in processing position sense. No one region examined, number or regions, nor combination of regions was more or less predictive of poor position match task performance. Others have questioned whether imaging data can assist in predicting the potential for therapy-driven improvements after stroke. Marshall et al (2009) acquired fMRI data 48 hours after stroke to investigate if early brain activation patterns could predict a subsequent change in motor performance. Their findings suggest that anatomy may set a limit on recovery, but that improvement of motor function was not solely related to the integrity of the corticospinal system. In fact, they found a pattern of activation in areas beyond their ROI – the postcentral gyrus and cingulate cortex – that appeared to be linked to motor recovery. This is in keeping with the knowledge that extensive circuitry exists between sensory and motor areas (Wolpert et al., 2013) and that sensory deficits can impact functional

performance (Dukelow et al., 2012). As such, the integrity of sensory regions is an essential consideration when attempting to make predictions about recovery after stroke.

#### **4.4 Study Limitations**

##### ***4.4.1 Brain Injury From Stroke Is Not Random***

A foundational issue exists with lesion analyses. Given the structure of the vascular system of the brain, injury caused by stroke is not random. Some brain regions are more likely to be damaged than others. The prime example occurs with middle cerebral artery (MCA) stroke. In addition to being the vessel most likely to be affected by ischemic stroke (Ng et al., 2007), it supplies a vast territory, perfusing the majority of the lateral surface of the cerebral hemisphere as well as the white matter for the hemisphere's convexity (Brust, 2013). In the case of our study, all of the major sensory structures excepting the thalamus and inferior PLIC are perfused by the MCA.

##### ***4.4.2 VLSM Is Unable To Analyze Interactions Among Brain Regions***

The VLSM lesion analysis method has limitations. First, in seeking a location integral to a particular behaviour, the assumption is made that discrete anatomical areas deal with specific functions. However, several behaviours appear to be carried out in a distributed manner, involving more than one brain area (Culham et al., 2003; Reichenbach et al., 2011). The question then is whether all, or just one, of those areas are essential for the behaviour being investigated. Further, VLSM is unable to determine the temporal sequence of information processing between these connections (Rorden and Karnath, 2004). Another issue facing lesion studies is that of individual variability. Subjects may have anatomical differences between subjects as well as

variable plastic changes after stroke between individuals (Amunts et al., 2004; Nudo et al., 1996).

#### ***4.4.3 Subjects With Mild/Moderate Strokes***

The subjects in our study mainly had mild/moderate stroke-related deficits. This is in part due to the requirements of the study: individuals were inpatients who had the capacity to volunteer, the ability to follow 3 step directions, and the stamina to complete two 45-minute assessments (the robotic and clinical assessments were each 45 minutes, but did not need to be completed consecutively). As a result, our sample may not represent those with more severe stroke or those with such mild strokes that hospitalization was unnecessary.

#### ***4.4.4 Time Difference Between Imaging Collection and Robotic Assessment***

The MRI and CT images were collected within 10 days of stroke symptom onset (median 1 day). The robotic position matching task was completed within 24 days (median 8 days). While attempts were made to recruit subjects as soon as possible after stroke, this was not always achievable. Some subjects were unavailable earlier because they were undergoing medical or diagnostic procedures, some were unwell, and some did not have the physical or cognitive stamina until days or weeks after the stroke onset. The possibility exists that the subjects' stroke may have progressed between the time of imaging collection and robotic assessment. Studies have demonstrated that stroke progression occurs in 9.8 – 33% of ischemic strokes within 48 to 72 hours after stroke onset (DeGraba et al., 1999; Sumer et al., 2003; Weimar et al., 2005). Stroke progression has been defined as "...progressive worsening of neurologic deficits" (Weimar et al., 2005) and may result from pathophysiological mechanisms such as extension of

original infarct, recurrence of local infarct or a new remote infarct, systemic inflammation, or brain edema (Kwan and Hand, 2006). The difference in time between imaging collection and robotic position matching assessment may introduce bias into our study. It is possible that stroke progression occurred in some subjects and thus the lesion on their MRI or CT may not fully account for the subject's performance in the robotic task.

#### ***4.4.5 Differing Reference Line for CT and MRI Scans***

It is common practice to use both MRI and CT scans in VLSM studies investigating the relationship between brain regions and behaviour after stroke (Karnath et al., 2011; Verdon et al., 2010). Using this methodology, lesions identified on CT scans are manually drawn onto a MRI template (which is in the Montreal Neurologic Institute stereotaxic space). The reference line for MRI's is the anterior/posterior commissure line while for CT's it is the inferior orbitomeatal line. This poses a challenge when relating the lesion location across the two types of scans as the anatomical features do not align perfectly and may be a potential source of error when drawing the lesions onto the template.

In the literature a gold standard method for aligning MRI and CT scans is lacking. We attempted to co-register the CT images to the same alignment as the MRI scans using SPM8; however, this resulted in a loss in definition (blurring of the images) such that it became very difficult to identify the lesions. Thus, for the CT scans, we carefully localized lesions with respect to anatomical landmarks in order to manually transpose them onto the MNI template provided with MRICron. A stroke neurologist verified all lesion markings. Finally, in the event that a subject

had more than one CT scan, we used the scan that was the latest time point within 10 days post stroke.

## **4.5 Future Directions**

### ***4.5.1 Interaction of Proprioception/Position Sense and Neglect***

Our study identified brain regions that are important for processing position sense, however, several of these areas have also been associated with hemispatial neglect after stroke. Occurring in approximately 23% of people after stroke (Pedersen et al., 1997), hemispatial neglect is defined as a deficit in processing or responding to sensory (visual, tactile, auditory, olfactory) stimuli on one side of space that is not due to a lack of sensation (Kerkhoff, 2001). It is most often associated with lesions to the right middle cerebral artery territory (Kerkhoff, 2001). A large number of VLSM studies have sought to identify the neuroanatomical correlates of various subtypes of neglect (Committeri et al., 2007; Karnath et al., 2004; Karnath et al., 2009; Karnath et al., 2011; Verdon et al., 2010). Differences exist in the findings depending on subtype of neglect studied, assessments used in the determination of neglect and, perhaps, due to sampling differences. In general, neglect was observed in association with right-sided damage to various combinations of the following structures: postcentral gyrus; supramarginal gyrus; inferior parietal lobule; dorsolateral prefrontal cortex; superior and middle temporal gyri; insula; putamen; and caudate (Committeri et al., 2007; Karnath et al., 2004; Karnath et al., 2009; Karnath et al., 2011; Verdon et al., 2010). Several of these areas were found to be associated with position sense deficits in our study. This is in keeping with previous observations that somatosensory deficits often co-occur with impairments in higher-order spatial processing such as neglect (Kerkhoff, 2001; Meador et al., 2002). Indeed, in our sample of 91 subjects, 22 had

neglect and 20 of these individuals failed the position match task (failed 2 or more parameters). Repeating this VLSM analysis without the neglect subjects would help differentiate the neural correlates of position sense and neglect. This has obvious implications for rehabilitation. These complex disorders are difficult to treat and the more we learn about them, the more equipped clinicians are to provide effective treatment. Further, as modalities like repetitive transcranial magnetic stimulation become more available for neglect treatment (Kerkhoff, 2003), identification of target structures is of utmost importance.

#### ***4.5.2 Lateralization***

In the present study, left hemisphere lesions were mirrored across the midsagittal axis in order to group all subjects to make final calculations. This methodology is typical of lesion analyses investigating motor function after stroke (Lo et al., 2010b; Zhu et al., 2010). In doing so, however, the importance of the right hemisphere for spatial awareness was not accounted for. The dominance of the right hemisphere for visuospatial orientation is well documented (Kerkhoff, 2001; Mesulam, 1999). Preliminary evidence exists for lateralization effects in somatosensory processing. Goble (2009) studied position sense in children with cerebral palsy and found more impairments in those with right hemisphere damage. Similar results have been found in adult stroke subjects for position sense (Dukelow et al., 2010) and kinesthesia (Semrau et al., 2012). Further, neuroimaging has demonstrated more activity in the right versus left fronto-parieto-temporal areas during tasks requiring kinesthetic processing (Naito et al., 2005). Though this study suggests that activity is differentially distributed across hemispheres, the key structures involved in kinesthetic perception were identified. In terms of our study, lateralization effects are an important consideration, however, the extent of their impact is unknown.

### ***4.5.3 Influence of the Cerebellum***

As discussed in the introduction, the spinocerebellum receives proprioceptive information from the upper limbs for motor control (section 1.2.1) (Gilman, 2002; Grant, 1962; Lisberger and Thach, 2012; Oscarsson and Uddenberg, 1964). Along with other somatosensory inputs, this information provides the cerebellum with constant updates about the body. Further, this information is transmitted to the cerebellum in two pathways: one responsible for providing sensory feedback of movements and the other for on-line movement control (Lisberger and Thach, 2012). The lateral cerebellar hemispheres have extensive cortical connections that subserve motor planning (Lisberger and Thach, 2012). Connections between these areas and the parietal cortex have been identified in monkeys (Dum and Strick, 2003) and have been hypothesized to play a role in sensory acquisition and refinement to inform the motor system (Manto et al., 2012). Cerebellar VLSM studies are less common than those investigating cortical areas. This is likely due to the fact that a normalized template has only recently been devised for the cerebellum (Diedrichsen, 2006). However, a study comparing position sense in the cerebellum and cortical structures would provide important information regarding the interaction between these two streams of proprioceptive information. This information could influence treatment strategies targeted at use of the less/non-damaged pathway.

### ***4.5.4 Implications for Treatment***

Researchers with access to valid, reliable and highly sensitive means of quantifying position sense deficits are positioned to identify and evaluate strategies treatment strategies targeted at proprioceptive deficits. As discussed previously, stroke rehabilitation has traditionally focussed on motor recovery. There are relatively few sensory intervention studies (Connell and Tyson,

2012; Schabrun and Hillier, 2009) and even fewer which investigate proprioceptive interventions specifically (Cambier et al., 2003; Carey et al., 1993; Smania et al., 2003; Yekutieli and Guttman, 1993). This is possibly related to limitations associated with clinical assessments and the resultant challenge in identifying deficits, inability to identify homogeneous study populations, and the lack of sensitivity to perceive change over time. These challenges can be addressed using our robotic position match task (Dukelow et al., 2010; Scott and Dukelow, 2011). Thus an important future direction is the use of this assessment to systematically evaluate current and novel proprioceptive treatments. Determination of evidence-based interventions targeted at the primary deficit (i.e. sensory versus motor) would presumably realize improved functional recovery after stroke.

#### **4.6 Conclusion**

At an estimated 50,000 cases annually, stroke is the leading cause of disability in Canada (Canada, 2009). Proprioceptive deficits, occurring in approximately 50% of stroke patients (Carey et al., 1996; Connell et al., 2008), contribute significantly to disability. Since proprioception plays a crucial role in the initiation and control of limb posture and movement (Sainburg, 1995; Scott, 2002), deficits are believed to impede upper extremity motor recovery (de Weerd et al., 1987; Mercier et al., 2004; Pavot et al., 1986; Wade et al., 1983) and thus independence. Those with proprioceptive deficits have been found to have longer inpatient stays and increased care requirements upon discharge (Chester and McLaren, 1989; Davidoff et al., 1991; Zeman and Yiannikas, 1989).

Unfortunately our clinical assessments fall short in quantifying proprioceptive deficits in stroke patients (Carey et al., 1996; Connell and Tyson, 2012; Garraway et al., 1976; Lincoln et al., 1991). This is believed to result in deficits going unchecked and untreated, thus interfering with optimal recovery. Without adequate measurement tools, quantifying proprioceptive change is not possible and rehabilitation is left without a “gold standard” treatment (Connell and Tyson, 2012; Doyle et al., 2010; Schabrun and Hillier, 2009).

Proprioception is comprised of at least three subcomponents and this complexity may contribute to assessment challenges. This study adopted Sherrington’s definition that proprioception is the sensory information resulting in a sense of self-position and movement without the use of vision (Sherrington, 1907).

We used a quantitative, reliable, and sensitive robotic position matching assessment in combination with a novel lesion analysis technique (VLSM) to identify neural correlates of one subcomponent of proprioception: position sense. Our VLSM analysis produced statistical maps for each of the 3 parameters of the position match task. Each map was different, indicating that each parameter represents related but slightly different features involved in the overall construct of position sense. A Region of Interest (ROI) analysis was used to provide another means of testing our hypothesis. Together, these analyses supported our hypothesis that damage to the VPL of the thalamus, the PLIC, the postcentral gyrus, and the posterior parietal association area are associated with position sense deficits. Additionally, damage to the inferior frontal lobe, insula, middle temporal gyrus, and superior temporal gyrus was associated with poor position sense scores. Therefore, a distributed network appears to be involved in processing upper

extremity position sense. Further, damage to a region of interest resulted in approximately a 50-60% chance of performing poorly the position match task, indicating that good behavioural assessments are a necessary compliment to imaging in the detection of position sense deficits. Together, these results provide new insights into the neural correlates of position sense, thus furthering our understanding of proprioceptive deficits resulting from stroke. Improved understanding of proprioceptive deficits is foundational for predicting sensorimotor recovery and guiding both acute management and therapeutic strategies by rehabilitation professionals.

#### **4.7 Contributions**

As the lead investigator in this thesis, I made the decision to pursue a new technique for our laboratory, Voxel-based Lesion-Symptom Mapping (VLSM). I was involved with the collection of data, performing all data analysis, and writing up the present thesis. However, a number of other individuals contributed to this project. My supervisor, Dr. Sean Dukelow, offered overall guidance during the development of my research project with contributions from my supervisory committee, Dr. Andrew Demchuk and Dr. Bradley Goodyear. Dr. Jamsheed Desai verified the lesion markings. Ms. Janice Yajure and Ms. Megan Metzler recruited subjects and administered the clinical and robotic assessments. Dr. Jennifer Semrau offered statistical support.

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