The Internal Representation of Arm Position

Revealed Through

The Spatial Pattern of Hand Location Estimation Errors

by

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of the Requirements for the Degree
Doctor of Philosophy

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ABSTRACT

Our ability to estimate the position of our body parts in space, a fundamentally proprioceptive process, is crucial for interacting with the environment and movement control. For proprioception to support these actions, the Central Nervous System has to rely on a stored internal representation of the body parts in space. However, relatively little is known about this internal representation of arm position. To this end, I developed a method to map proprioceptive estimates of hand location across a 2-d workspace. In this task, I moved each subject's hand to a target location while the subject's eyes were closed. After returning the hand, subjects opened their eyes to verbally report the location of where their fingertip had been. Then, I reconstructed and analyzed the spatial structure of the pattern of estimation errors. In the first couple of experiments I probed the structure and stability of the pattern of errors by manipulating the hand used and tactile feedback provided when the hand was at each target location. I found that the resulting pattern of errors was systematically stable across conditions for each subject, subject-specific, and not uniform across the workspace. These findings suggest that the observed structure of pattern of errors has been constructed through experience, which has resulted in a systematically stable internal representation of arm location. Moreover, this representation is continuously being calibrated across the workspace. In the next two experiments, I aimed to probe the calibration of this structure. To this end, I used two different perturbation paradigms: 1) a virtual reality visuomotor adaptation to induce a local perturbation, 2) and a standard
prism adaptation paradigm to induce a global perturbation. I found that the magnitude of the errors significantly increased to a similar extent after each perturbation. This small effect indicates that proprioception is recalibrated to a similar extent regardless of how the perturbation is introduced, suggesting that sensory and motor changes may be two independent processes arising from the perturbation. Moreover, I propose that the internal representation of arm location might be constructed with a global solution and not capable of local changes.
DEDICATION

I owe much gratitude to my family for this accomplishment. Thanks to my uncles and aunt: Heriberto Gonzalez, Jose Gonzalez, Luis Gonzalez, and Monica Gonzalez, I was able to go finish undergrad. I will forever be thankful for their help and support during those difficult times. I would like to thank my parents for their unconditional support, love, and motivation throughout my life. I thank my brothers for their constant support and watching over me. Finally, I would like to thank the Kothrade family who made it possible for me to continue my education.

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Additionally, I owe much of my growth as a scientist to my mentor and advisor Dr. Stephen Helms Tillery. Particularly, I appreciate the confidence he instilled on me as well as the freedom he gave me to pursue my own ideas. Nonetheless, his vision and ideas were essential in this work. His guidance shaped this thesis into something that I am very proud of. His excitement about science was contagious and kept me motivated. I would also like to thank Dr. Christopher Buneo for his guidance and support in the last few years of this work. His advice and different point of view provided valuable insight and perspective. I would like to thank the rest of the committee members: Dr. Marco Santello, Dr. Veronica Santos and Dr. Jeffrey Kleim for their support, ideas, and valuable feedback. I would also like to thank Dr.
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6.1. Similarity of pattern of errors across time for an exemplary subject

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The studies presented in this thesis explored the structure of the internal representation of arm position. Our sense of limb position, a fundamentally proprioceptive process, is crucial for interacting with the environment and movement control. It follows that for proprioception to support those actions, it must rely on an internal representation of the body parts in space. This thesis explored this internal representation in detail by focusing on its structure and stability. To this end, we developed a novel method to map proprioceptive estimates of hand location across a 2-dimensional workspace, which allowed us to construct a spatial pattern of estimation errors. Although multiple investigators have examined the ability of subjects to estimate the location of their hands in space, relatively little is known about the resulting spatial structure of the estimation errors. Since errors for individual subjects in these tasks are usually large, variable, and idiosyncratic, single subject analyses are usually not carried out. Here, we analyzed the magnitude and direction of the resulting errors at the single-subject level and on the pooled data across subjects.

The study described in Chapter Two examined the structure of the pattern of estimation errors in detail. Although this structure has not been analyzed in this way before, casual observations from hand estimation studies have suggested that subjects make systematic yet subject-specific errors when estimating hand position in space. Yet, analyses of the errors tend to focus on generalized effects across subjects. If these patterns are truly idiosyncratic, then single-subject analyses need to be performed as well. It is
not surprising then that the spatial structure of estimation errors of individual subjects has not been analyzed in detail. Additionally, most of these hand estimation studies recruit right-handed subjects who perform the experiments with their dominant hand only. If these patterns are subject specific, then the hand tested might have an effect on the structure of the map.

In this chapter, we focused on the effect of tactile feedback and hand used on the resulting pattern of errors. Studies that have probed the interaction between proprioception and touch have suggested a two-way relationship: tactile feedback helps proprioceptive signals in enhancing endpoint accuracy while proprioception can clearly affect tactile perception. It remains unclear how the relationship between touch and proprioception contributes to the structure of the internal representations of arm location. We wondered whether touch could affect the perception of limb position and thus change the structure of the proprioceptive map. Additionally, we wondered whether the reported systematic pattern of errors would be similar across hands and whether any effects due to touch would also be symmetric.

Using the hand estimation task we developed, we mapped proprioception at 100 locations across the workspace while manipulating two variables: tactile feedback (touch or no touch) and hand used (right or left hand). Subjects performed 4 different experiments: right hand · touch, right hand · no touch, left hand · touch, and left hand · no touch. We found that neither the hand used nor tactile feedback affected the overall structure of the map. Only touching the table with the right hand, regardless of hand
dominance, decreased the magnitude of the errors. In addition, we found that
the pattern of errors was different between subjects and not uniform across
the workspace. These results support previous observations that the errors in
hand estimation tasks are systematic yet subject-specific and non-uniform
across the workspace. Additionally, these results suggest that receiving
tactile feedback enhances our perception of where our arm is in space, but it
does not necessarily affect or change this perception. The proprioceptive map
of arm location is stable.

The study described in Chapter Three furthered explored the role of
tactile signals on the structure of the proprioceptive map by incorporating
electrotactile feedback as one of the experimental conditions. In a recent
study, electrotactile stimulation to the fingertips was provided to elicit a
tactile illusion, which was eliminated when subjects adopted specific hand
postures. This study suggests that tactile perception is modulated by
proprioceptive inputs. We have previously reported in Chapter Two that
touch did not affect the structure of the proprioceptive map, so here we
wondered whether the completely artificial sensation induced by
electrotactile stimulation could affect the pattern of errors. On the other
hand, if electrotactile stimulation does not have an effect on the direction of
the errors, then this would suggest that proprioception provides a stable
underlying map that modulates tactile perception.

Again using the estimation task, we manipulated the type of tactile
feedback subjects received when their hands were at each target location:
touch, no touch, or electrotactile stimulation. In order to provide electrotactile
stimulation, we attached a small electrode to the volar aspect of the right index fingertip, which provided a short pulse of current when subjects’ fingertip was above (not touching) a target. In this experiment only right-handed subjects participated and only their dominant hand was tested. We found that electrotactile stimulation did not affect the direction or magnitude of the estimation errors. Therefore, these results further suggest that subjects estimate the location of their hands using a stable proprioceptive representation of their arms, one which is not spatially affected by touch.

The experiment in Chapter Four aimed to test the extent of the stability of the map by perturbing the subject’s sense of limb position through a visuomotor adaptation. It has been previously shown that proprioception can be recalibrated in the direction of the distortion following different visuomotor adaptations (Cressman & Henriques, 2009; Ostry, Darainy, Mattar, Wong, & Gribble, 2010). Therefore, a visuomotor adaptation should lead to a change of the internal representation of the body’s position in space. In Chapter Two, we observed that the pattern of errors was stable for each subject but not uniform across the workspace. So here we hypothesized that perturbing the map would result in a non-uniform pattern of adaptation, in which some areas of the workspace would be more robust to the perturbation than others.

For this experiment subjects participated in two sessions completed on two different days. On the first session, subjects completed the first baseline of the hand estimation task. On the second session, which took place 3-5 days later, subjects performed the second baseline of the hand estimation task as
well as the post perturbation hand estimation task. Then we compared the pattern of errors post perturbation to those of pre perturbation to determine if subjects’ estimations were affected by the adaptation. The visuomotor adaptation was achieved by having subjects reach to a single target location on the 2-dimensional surface of a horizontal table while we provided misaligned visual feedback of the finger movement. Subjects could not see their hands or the target directly but instead they saw a virtual target and a cursor that represented their moving finger displayed on a vertical computer monitor located in front of their working space. Here we induced a local perturbation to a single location on the workspace by gradually displacing the cursor representing their finger 1 mm to the left of the target on every reach. The misaligned visual feedback of the location of the cursor that represented the subjects’ finger prompted the subjects to adapt their reaches to the right of the target in order to reach the target. Unbeknownst to the subjects, they were reaching 5 cm to the right of the target by the end of the perturbation.

We found that the visuomotor adaptation had a significant effect on the magnitude and direction of estimation errors when we analyzed the pooled data across subjects and target locations. However, we were unable to test our hypothesis that there would be some areas of the workspace that would be more robust to the perturbation than others. We found that the magnitude of the adaptation was smaller than the intrinsic variability in the maps. Therefore, the resulting adaptation (2.5 cm) might have not being strong enough for the effect to be distinguishable from the noise in the system.
In addition, there were some limitations of the experiment that might have contributed to the small magnitude of the effect. Therefore, we decided to replicate the experiment with a more robust perturbation, which we expected would induce a greater effect on the map. In addition, we aimed to address the limitations by better controlling some aspects of the experimental conditions.

In Chapter Five we aimed to induce a stronger perturbation to the proprioceptive map by using a prism adaptation. Prism adaptation is known to create a global realignment of the visual-motor and proprioceptive-motor internal coordinates that results in a spatial realignment of proprioception (Redding, Rossetti, & Wallace, 2005). Thus, a strong and global perturbation would allow us to test our hypothesis that the calibration of the internal representation of hand location is non-uniform across the workspace, which will have areas that are more robust than others to the perturbation.

Similar to the experimental paradigm in Chapter Four, subjects performed the hand estimation task twice as a baseline measure and once after the prism adaptation. Then we compared the pattern of errors post perturbation to those of pre perturbation to determine if subjects’ estimations were affected by the adaptation. During the prism exposure, subjects wore prism goggles that displaced their vision 11.4° to the left while pointing towards a target located 100 cm in front of them. This time all tasks were performed during the same session. We found that subjects adapted 5 cm to the induced perturbation (20 cm), which was double the adaptation observed after the visuomotor adaptation. In agreement with the results in Chapter
Four, we observed that the prism adaptation had a significant effect on the magnitude and direction of estimation errors when we analyzed the pooled data across subjects and target locations. In addition, we were unable to find significant effects at the single-subject and single-target level. Surprisingly, the observed effects on the proprioceptive map were of a similar magnitude as those observed in Chapter Four. This small effect indicates that proprioception is recalibrated to a similar extent regardless of how the perturbation is introduced, suggesting that sensory and motor changes may be two independent processes arising from the perturbation. This result is in agreement with recent studies by Henriques and her group (Cressman & Henriques, 2010; Jones, Cressman, & Henriques, 2009; Salomonczyk, Cressman, & Henriques, 2011) in which they used different experimental manipulations of the visuomotor adaptation paradigm and found no significant correlation between proprioceptive recalibration and the level of motor adaptation. Yet, we are the first group to our knowledge to probe proprioception with both a global perturbation (prism adaptation) and a local perturbation (visuomotor adaptation). Since the local perturbation affected the map in a similar way as the global perturbation did, we suggest that the proprioceptive map of hand location might be constructed with a global solution instead of being composed of a set of local maps.

Finally, Appendix C is an overview of the project I worked on during the first two years of the doctorate. The purpose was to investigate an alternative to intracortical microstimulation for brain stimulation to provide somatosensory feedback to a prosthetic device. The problem with intracortical
microstimulation is its poor long-term reliability, limited cell specificity, and low spatial resolution. To address those issues, we proposed to use light stimulation of genetically modified cortical neurons. Optogenetic tools such as Channelrhodopsin-2 (ChR-2) have the potential of long-term reliability, cell-specificity, and fast kinetics. ChR-2 is a light sensitive protein that induces temporally precise depolarization of the cell membrane when activated with blue light at low intensities. Currently, in vivo studies using ChR-2 rely on invasive light sources that provide little or no capability for patterned activation. These light sources typically rely on traditional LEDs of fiber-optic coupled diode lasers. I proposed to use Organic Light Emitting Diodes (OLEDs) as the light source for non-invasive patterned activation of the cortex. OLEDs differ from traditional LEDs in that their emissive electroluminescent layer is composed of a thin organic film placed between two electrodes. These organic compounds allow the design of flexible, easily customizable, and ultra-thin displays that have extremely high fluorescent efficiencies, resolutions and fast switching times.

In this Appendix, we demonstrated in vitro activation of Channelrhodopsin-2 neurons using a novel light source. Our goal was to stimulate ChR-2 cells in vitro in a pattern of activity, and eventually ChR-2 cells in vivo using an OLED display. We recorded photocurrents in dissociated currents of ChR-2 positive cells using an OLED. In addition, we induced front limb movements in a lightly anesthetized mouse when stimulating left motor cortex with a fiber optic as a proof that we could replicate studies in the literature. These findings are one step closer towards

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developing an OLED display capable of stimulating the somatosensory cortex in patterns of activity to provide sensorimotor feedback from the prosthetic.
Chapter 1

BACKGROUND

Proprioception, the ability to estimate the location of our bodies and limbs in space, is critical for perception and action as it allows us to interact with people and objects in our environment. Although proprioception relies on afferent signals, perceiving the location of body parts in space must also rely on information about the size and shape of the body segments between joints. However, neither tactile nor proprioceptive receptors provide such information about body size. Thus, perceiving limb position in space must also rely on a stored representation of the body’s metric properties. In addition, this stored representation is used to provide information about the current state of the body to perform actions. Computational studies on sensorimotor integration suggest that instead of using a single perceptual and motor snapshot to provide information about the current state of both the world and one’s own body, an internal estimate of this state is maintained and updated by current sensory and motor signals (Wolpert, Ghahramani, & Jordan, 1995; Wolpert, Goodbody, & Husain, 1998). This suggests that there is an internal representation of our body parts in space, which is stable but is continuously being calibrated based on incoming sensory and motor signals. Studying the errors subjects make when estimating hand location in space might provide insight into the structure of this internal representation. To this end, this thesis explored this internal representation in detail by focusing on its structure and stability through the study of the spatial pattern of hand location estimation errors.
PHYSIOLOGY OF CODING LIMB POSITION

The central nervous system uses information from several sensors to determine limb position and movement. Sensors that can provide information about active and passive changes in limb position include muscle spindles, tendon organs, joint receptors, and cutaneous touch receptors. It was originally thought that the only sensors involved in determining limb position and movement were receptors in muscles, joints, and ligaments, however skin receptors invariably respond to the stretching of the skin that occurs during limb movement (Nelson, 2002).

Muscle Spindles. These organs play a primary role for the position sense of the body as shown by vibration-induced illusions of movements elicited by manipulating the activation of these organs (Roll & Vedel, 1982). Muscle spindles are one of the two types of slowly adapting mechanoreceptors found in muscles, which lie in parallel to the main muscle fibers. They measure muscle stretch and rate of change of stretch in all skeletal muscles. Neck muscles and intrinsic muscles of the hand have a particularly high concentration of these sensors, which contribute to controlling posture and fine manipulations (Rossi-Durand, 2006). The structure of a muscle spindle consists of 2-12 intrafusal muscle fibers encased in a fluid-filled capsule and attached at each end to the surrounding extrafusal muscle fiber. This capsule has two narrow extremities and one wider middle part, which contains and protects all the nuclei. Typical muscle spindles contain three types of intrafusal fibers: a dynamic bag1, a static bag2, and 2-11 chain fibers (Nelson, 2002; Rossi-Durand, 2006). These fibers receive innervations by
sensory and motor fibers: one large primary sensory fiber (Group Ia), 0-5 intermediate secondary sensory fibers (Group II), and 6-12 small diameter motor fibers (gamma and beta motor neurons) (Clark & Horch, 1986). Primary fibers have a rapidly adapting response to changes in muscle length that provides information about limb velocity and direction of movement. Secondary fibers mainly respond to static stretches and thus provide information about the static position of limbs. Since multiple motor fibers innervate the individual intrafusal fibers, individual segments are controlled by the Central Nervous System (CNS), which provides a fine control of the mechanical properties of the fiber. In addition, the activation of the gamma and beta motor neurons can modify muscle spindle sensitivity. In summary, the reason why muscle spindles play a primary role for the position sense and movement of the body parts is because they supply the CNS with information about muscle state and lengthening while the CNS controls the muscle’s mechanical stretch-sensitivity.

**Golgi Tendon.** Golgi tendons are one of the two types of slowly adapting mechanoreceptors found in muscles, which lie in series with the main muscle fibers. They measure the tension produced in the muscle during stretch. These organs are located between muscles and tendons, and consist of encapsulated bundles of small tendon fascicles. A single large diameter group Ib afferent fiber, which responds to stretch of the tendon fascicles, innervates them. Since a single Golgi organ monitors multiple muscle fibers from different motor units, information from the multiple Golgi tendons found at one junction provides ample sampling of the tension developed in
the muscle. As these organs only respond to muscle tension, it is still not clear what their contribution to position sense is. This could be due to lack of evidence as most of the studies since Sherrington have focused on the role of muscle spindles on proprioception neglecting the role of Golgi tendons. A recent modeling study has suggested that muscle spindles have poor control of joint position and movement in the absence of information about tendon length, which is provided by Golgi tendons (Kistemaker, Wong, & Gribble, 2012).

**Joint Receptors.** Joint receptors were originally thought to be the primary source of proprioceptive information about limb position and movement because they were believed to signal joint position over the full range of motion (Clark & Horch, 1986). Eventually, experiments showed that these receptors mostly fired at the extreme positions of the joint and were thus unlikely to provide information about limb position. Although some joint receptors provide information about mid-range movement, the number of muscle and skin receptors that fire in this range is greater (Nelson, 2002). Therefore, it is currently believed that these receptors signal joint movement, act as joint limit detectors, and even as nociceptors, but are unlikely to play a major role in the sense of position (Proske, Schaible, & Schmidt, 1988).

Perhaps their role is to prevent damage to the joint by signaling tension in the capsule and ligaments as the joint approaches the limits of normal joint movements. Other evidence as to their minor role in proprioception comes from studies with patients who had their finger or hip joints replaced with no evident effect on their joint position sense (Clark & Horch, 1986).
**Skin Receptors.** Skin receptors are thought to contribute to proprioception as they are activated when the skin around a joint is stretched during most limb movements. Based on the density of these receptors on the skin they surely play a role on proprioception. For comparison, there are about 17000 skin mechanoreceptors on the surface of the hand alone while the whole arm contains about 4000 muscle spindles, 2500 tendon organs, and a few hundred joint receptors (Nelson, 2002). The skin contains both slowly and rapidly adapting mechanoreceptors, which could signal joint position and movement, respectively. Slowly adapting receptors such as Ruffini afferents and Merkel cell afferents continue to fire with maintained deformation of the skin, which could provide information about the static position of the joint. However, these afferents make up a small proportion of the total receptors on the skin and thus their contribution to proprioception might not be significant. In that case, rapidly adapting receptors would play a bigger role in proprioception since they make up a larger proportion of the total receptors. Studies have shown that both type of receptors play a role in proprioception: slowly adapting afferents on the hand showed dynamic and static sensitivity to skin stretch (Edin, 1992) while rapidly adapting afferents on the hand responded to skin strain changes (Edin, 2004). In addition, a recent study showed that not only skin receptors on the hand contribute to proprioception but also receptors in the elbow and knee (Collins, 2005). Similarly, facial cutaneous receptors have been shown to provide proprioceptive information crucial for speech production and perception (Ito, Tiede, & Ostry, 2009).
SENSE OF TOUCH

Receptors involved in the sense of touch directly provide information about mechanical interactions and are thus termed mechanoreceptors. They are crucial in the control of dexterous manipulation of objects, which is supported by the massive population of receptors found in the fingertips and palms. There are about 2000 mechanoreceptors in each fingertip and about 10000 mechanoreceptors in the glabrous skin on the volar surface of the rest of the hand (Johansson & Flanagan, 2007). Knowledge of the contribution of different receptor types to the sense of touch comes mainly from studies on the glabrous portions of the hand, which is specialized for providing a neural image of the objects we manipulate. The four receptor-types innervating the skin are Merkel cells, Meissner corpuscles, Pacinian afferents, and Ruffini afferents. These receptors are classified as type I or type II depending on the depth of the cell beneath the skin. Type I afferents are located at the dermal-epidermal margin while type II afferents terminate in the deeper dermal and sub-dermal tissues (Johansson & Flanagan, 2007). They are also classified as rapidly or slowly adapting depending on their rate of adaptation to stimuli. Rapidly adapting afferents respond only during dynamic phases of tissue deformation while slowly adapting afferents respond to sustained skin deformation with a graded sustained discharge (Johansson & Flanagan, 2007).

**Merkel Cell Afferents.** These cells consist of slowly adapting type I (SA-I) afferents because they respond to sustained skin deformation and are located closer to the surface. However, they are much more sensitive to skin
movement than to static deformation. They can resolve spatial details of 0.5 mm and are very sensitive to edges, points, corners, and curvature. These afferents innervate the tip of the epidermis and have small receptive fields. One important property of these receptors is their surround suppression, which makes them sensitive to local stimulation and insensitive to a uniform skin indentation (Nelson, 2002). Therefore, these mechanoreceptors are responsible for form and texture perception.

**Meissner Cell Afferents.** These cells consist of rapidly adapting type I (RA-I) fibers. They are located closer to the skin surface and innervate the skin more densely than any other mechanoreceptor type. This may result in their greater sensitivity to skin deformation compared to Merkel cell afferents. However, they have a large receptive field that results in poor spatial resolution (3 mm) (Nelson, 2002). Therefore, they are well suited for the perception of events that produce low frequency and low-amplitude skin motion such as low frequency vibrations and grip control (Nelson, 2002).

**Pacinian Afferents.** Pacinian afferents end in single Pacinian corpuscles, which are located deep in the dermis. They are rapidly adapting type II (RA-II) fibers that respond to high frequency stimulation. They are extremely sensitive due to the unmylinated endings and larger receptive fields: they respond to displacements as small as 10 nm (Nelson, 2002). These corpuscles are composed of multiple layers of fluid-filled membranes, which act as high-pass filters. Some Pacinian afferents have receptive fields as big as the entire hand or arm and as small as a phalanx. Therefore, they are well
suited to detect vibrations in objects or tools held in the hand but not to provide spatial properties of a stimulus.

**Ruffini Afferents.** These are slowly adapting type II (SA-II) fibers located in the deep layers of the skin. They are different from the slowly adapting Merkel afferents because they have a significant larger receptive field with no clear borders. They are less sensitive to cutaneous indentation but more sensitive to skin stretch. These afferents sense directional strain such as shear strain produced by tangential forces to the skin when manipulating objects (Johansson & Flanagan, 2007). Therefore they are well suited to perceive hand configuration and direction of motion of an object moving across the skin.

**PSYCHOPHYSICS OF PROPRIOCEPTION: PERCEPTION OF LIMB POSITION**

Psychophysics of proprioception has been carried out in many different ways. All tests require subjects to indicate the perceived location of their arm in response to the presentation of the target position by the experimenter. There are different methods that have been employed to present the target position: passive, active, visual, and verbal. In the passive placement, the experimenter or a robot arm moves the subject’s arm to the desired position. In the active positioning, the subject moves his or her own arm to the desired position. In the visual placement, the subject views the desired position. In the verbal presentation, the experimenter verbally indicates the location of the desired location. Similarly, the subject identifies the perceived location of their arm using passive positioning, active
positioning, pointing, visual indication, and verbal indication. In the passive positioning, the subject’s arm is passively moved to a location where the subject makes a judgment based on the target presentation position. In the active positioning, the subject moves his or her arm to indicate or match the target position. In the active pointing, the subject uses a pointer or cursor to indicate the target position. In the visual and verbal indication, the subject verbally indicates the target position. The problem, however, is that proprioception is difficult to isolate. Depending on the experimental condition, there might be a transformation between coordinate frames, interhemispheric transfer of information, motor response due to active reaching, or a memory component.

An exemplary study on the estimation of hand location used a combination of the methods described above. In this study, van Beers and colleagues (1998) investigated the precision of proprioception based on three sources of information: proprioceptive information about the right hand, proprioceptive information about the left hand, and visual information (van Beers, Sittig, & van der Gon, 1998). In their task, subjects had to match the location of a visual target presented on the surface of a table by touching the underside of the table with either their right or left hand. In the third condition, subjects had to match the location of their right hand on the table with the left hand under the table. By deriving spatial distributions for proprioceptive localization and visual localization, the authors demonstrated that proprioceptive localization was more accurate in the radial direction than in the azimuthal direction while visual localization was more accurate.
in the azimuth than in the radial direction. The significance of their results comes from the fact that they were able to isolate each source of information through their regression analysis. However, their analyses did not account for the coordinate transformations or interhemispheric transfer of information, which could have resulted in different processing and noise. In addition, the authors warned about other possible factors that might have influenced their results: simultaneous tactile feedback, active arm movements, effect of time, starting position, and movement speed. This study highlights the difficulty of isolating proprioception. It also highlights that when visual information is available to aid in estimating hand location, the precision of the estimates are different than in the absence of vision.

Another exemplary study used different methods that avoided interhemispheric transfer of information and active reaching during the target position presentation to investigate coordinate transformations. In their study, Helms Tillery and colleagues (1991), aimed to determine the coordinate frame in which information from visual and kinesthetic signals was combined (Helms Tillery, Flanders, & Soechting, 1991). In their task, the experimenter presented the targets either visually or kinesthetically (passively displacing the subjects hand). After a brief period, subjects were asked to reach with the same hand to where the target or their hand had been. Due to the large estimation errors when subjects relied on proprioception alone, the experimenters concluded that subjects were unable to synthesize an estimate of the spatial location of the hand based solely on proprioceptive information. Estimations were better with a combination of
vision and proprioception. However, there is still the need to study proprioception on its own to fully understand how reliable it is on its own.

Recently, a study aimed to study proprioceptive sense by avoiding non-proprioceptive modalities (Wilson, Wong, & Gribble, 2010). In their task, a servo robot passively moved the subject’s arm to a reference position on the workspace. After a distractor movement, the hand was moved to a judgment position where the subject had to judge the current location of the hand with respect to the remembered proprioceptive reference location. This judgment was completely based on proprioceptive information as no visual feedback of the reference or judgment position was provided. However, they wondered if memory of the hand location at the reference location had an effect on the estimates. To this end, they replicated the experiment with the addition of a visual target representing the reference location where their hand had been. This novel method allowed them to systematically measure proprioceptive bias and acuity across 9 locations on a horizontal surface without coordinate transformations, interhemispheric transfer or active movements. They reported that both proprioceptive and visual-proprioceptive estimations yielded very similar qualitatively results. However, visual localization of the hand resulted in larger biases. The reason for this could have been that subjects estimated hand position based on competing information from proprioception and vision, which could have been perceived as misaligned due to the lack of depth cues. The significance of this study is that they are one of the few groups to map proprioception across the reachable workspace. The
limitation of their method is the inability to measure the direction of the subjects' estimations and thus to construct a spatial pattern of errors.

Being able to construct a spatial pattern of errors from the subjects’ estimations is of particular importance for the studies included in this thesis. The estimation task we developed tried to address some of these issues while still allowing us to construct pattern of estimation errors. Our task does not involve active movements or interhemispheric transfer of information but it does require a coordinate transformation when subjects report the location of their hands.

**SPATIAL REPRESENTATIONS**

Sensory systems map spatial representations of the external world in the brain. Peripheral receptor representations are maintained and reproduced as a map on the sensory cortices. This is true for touch, vision, audition and even olfaction.

**Somatotopic Map.** Somatotopic maps of touch refer to spatial correspondence between cutaneous receptor fields on the skin and neurons on each of the four areas of primary somatosensory cortex. Our knowledge of this somatotopic organization comes from receptive field mapping studies in which mechanoreceptors on the skin were stimulated while their corresponding cortical activation was recorded. A salient feature of these maps is that they do not represent the body in its actual proportions. The proportions of the cortical representations represent the density of receptors on the skin. Areas with a high density of receptors such as the hands and lips have a larger cortical representation.
Retinotopic Map. Retinotopic maps of vision refer to the spatial relationship of ganglion cells in the retina that project in an orderly fashion to the lateral geniculate nucleus and from there to the primary visual cortex. Since the visual field of both eyes overlap, these visual fields are thus integrated to form a coherent map of individual points in space. It follows that damage to specific regions of the visual cortex would cause visual deficits at specific locations on the visual field. As in the somatosensory cortex, the retinotopic representation in the cortical areas is distorted, which reflects the density of receptors and sensory axons at the periphery. The binocular portion of the visual fields is represented over a disproportionally large part of the caudal portion of the lobe, while the monocular portion is represented over a smaller region and is found in the anterior portion of the lobe.

Tonotopic Map. Tonotopic maps of audition refer to the systematic representation of sound frequency that is maintained throughout the central auditory pathways. This topographical representation of frequency starts in the cochlea, where the basilar membrane vibrates differently based on the frequency of the sound. Then it projects to the cochlear nuclei, inferior colliculus, and from there to the thalamus and the primary auditory cortex. At the inferior colliculus, this map is used for spatial localization.

Chemical Space. Although the olfactory system does not code any spatial information, it uses spatial segregation to encode the quality of an odorant. Neurons in the olfactory cortex are arranged by the type of receptor they possess and not by the spatial location of the receptors on the olfactory epithelium.
**Topographic Map of Proprioception.** Currently there is no report of a topographic representation of proprioception comparable to the topographic representations outlined above. In other words, there is no evidence that the spatial distribution of proprioceptors on the periphery is maintained or represented in primary somatosensory cortex. This is perhaps due to the complexity of proprioceptive signals, which are ultimately integrated to represent limb position and movement. An example of this complexity comes from neurons in primary somatosensory cortex that code limb position/arm movement and cutaneous receptors (D. A. D. Cohen, Prud’homme, & Kalaska, 1994; Rincon-Gonzalez, Warren, Meller, & Helms Tillery, 2011b; Ro, Debowy, Ghosh, & Gardner, 2000; Weber et al., 2011). It follows that it would be more behaviorally relevant to have a spatial map of limb position than a spatial map of the proprioceptors. Perhaps the internal representation of limb position is coded on a computational map and not on a topographic map.

**COMPUTATIONAL MAPS**

Unlike a topographic map, a computational map is organized in a manner not present in the periphery. This map is constructed by neural computations of more than one source of information. A computational map is an array of neurons acting as preset processors or filters that sort and evaluate multiple sources of information that are of biological importance (Knudsen, Lac, & Esterly, 1987). Each array in this map is tuned slightly differently resulting in systematic variations in the transformation of information. Some of the fundamental properties of computational maps are
that they are broadly tuned for the mapped parameter, their computations are preset, and they represent an intermediate step in processing information (Knudsen et al., 1987). Being broadly tuned means neurons throughout the entire map will be active at some level, in which some neurons will respond maximally and others will respond weakly to the same stimulus. However, due to the slightly different tuning of each array of neurons, the relative responses of the neurons provide high-resolution information about the mapped parameter. The neurons in the map perform preset computations, which mean that they do not need input from higher centers but rely on their intrinsic patterns of connectivity. Moreover, this intrinsic pattern of connectivity is not just genetically determined at some level but highly influenced by experience. It follows that the computations from this map are processed rapidly and can be accessed readily by higher order centers. Finally, a computational map evaluates crucial information that will be used by other centers in the nervous system.

The above description could certainly apply to an internal representation of limb position. In this representation, different neurons would be tuned to specific arm orientations (joint angles, skin stretch, muscle receptors) while the whole neuron population would yield in a systematic representation of limb position across the workspace. The intrinsic connectivity of this map would have been constructed by both genetics and experience, which would be evident from both its common themes across subjects and idiosyncrasies. In addition, this computational map of limb position would be used for subsequent processing such as movement control.
Finally, this map would not be a topographic representation of proprioceptors but would represent the integration of multiple sources of information such as mechanoreceptors on the skin, muscle spindles, joint receptors, Golgi organs, muscle efferents, etc. However, such a computational map for limb position in space has not yet been characterized.

Detecting computational maps can be difficult since neurons are usually tuned for multiple parameters and their response properties are complex. The complexity of the topography can also make it difficult to detect maps. Not only can the maps be difficult to access due to the topography, but also they can be as small as a cortical column. Nonetheless, a few computational maps have been found within the retinotopic and tonotopic maps (Knudsen et al., 1987). The line orientation preference map, which codes the angle of tilt of a line stimulus, is found in the visual cortex. A map of movement direction is found in the visual cortical area V5/MT. Similarly, several maps in the primary auditory cortex have been shown to provide spatial sound analysis: interaural delay map, interaural intensity difference map, and sound source location map. In addition, visual and auditory spatial maps are found in the superior and inferior colliculi, respectively. These maps process information to guide behavior such as turning towards visual or auditory stimuli.

**INTERNAL REPRESENTATIONS OF THE BODY**

An interesting line of evidence as to the existence of a computational map or higher order representation of limb position comes from cortical lesion studies. Over a hundred years ago, Head and Holmes (1911) aimed to
understand the processes underlying perception through the study of cerebral lesions (Head & Holmes, 1911). They proposed the existence of a body schema, which they described as an internal representation of the body posture mainly constructed from proprioception and tactile inputs. After over a century of disagreement on the definition and meaning of body schema, Paillard (1999) revisited this concept on his study of deafferented patients (Paillard, 1999). In their study, patients without proprioception had deficits to their body schema. They suggested that the location of body parts in space is represented in a sensorimotor mapping of the body space for which proprioceptive information is crucial. Similar to the two-stream hypothesis in vision that states the existence of two visual systems, one for object perception (what component) and one for spatial localization (where component) (Ungerer & Mishkin, 1982); this body schema would represent the where component. So this body schema would represent an internal representation of limb position. In addition to lesion studies, a recent review by Berlucchi and Aglioti (2010) discussed new neuroimaging, neurophysiological, and theoretical evidence of cortical areas specialized for the processing of the body schema (Berlucchi & Aglioti, 2010). Based on the multiple cortical areas found to represent some sort of body representation, they suggested the existence of multiple representations of the body and levels in the perception and knowledge of the body. They add that it is unlikely that these body-related brain areas are a direct representation of the body itself much like the topographic representations outlined above. Finally, they reiterate that relatively little is known about these representations and
thus there is still much to be determined about the neural mechanisms of these structures and maps.

In agreement with the idea that there are multiple representations, Medina et al. (2010) and Longo et al. (2010) proposed that the prevalent concept of body schema was too simplistic and thus divided it into three components: 1) primary somatotopic representation of cutaneous receptors, 2) a representation that encodes the body metrics: size and shape 3) a map that represents limb position derived from proprioception (Longo, Azañón, & Haggard, 2010; Medina & Coslett, 2010). They argued that there had to be an internal representation coding the body metrics since sensory afferent provides no information about the body length and shape. Therefore, they figured that for someone to be able to localize the spatial location of a tactile stimulus on the skin, the CNS must integrate these three representations. In other words, for someone to use his left hand to swat a fly that landed on his right forearm, his brain would first compute the sensation of the fly on the skin. Then, his brain would figure out the location of this sensation on the arm by using an internal map of the body metrics. Finally, his brain would compute the location of the right arm in space and then integrate this posture representation with the output from the previous computation. Relevant to this thesis is the idea of an internal representation of limb position or postural representation, which might include both the second and third representations described above.

A group recently investigated the internal representation of the body’s metric properties that underlies position sense (Longo & Haggard, 2010a).
Longo and Haggard (2010) developed a technique to isolate and measure the subjects’ perception of their hand’s size and shape. They did this by comparing landmarks on one body part (the hand) instead of comparing the actual vs. the perceived location of that body part in space. They showed that the hand representation was systematically distorted and not idiosyncratic. Instead, these representations retained some characteristics of primary somatosensory representations that were common across subjects. These results suggest that the somatotopic representation of the hand was integrated with the representation of the body’s metrics. In addition, they suggested that these distortions contribute to the systematic localization errors observed during hand estimation studies involving passive arm movements like the ones described in this thesis or in Helms Tillery et al. 1994 (described in section 1.2.3.). This would suggest that the representations of body’s metrics and limb posture are involved in our task.
Chapter 2

THE PROPRIOCEPTIVE MAP OF THE ARM

This entire chapter has been previously published in PLOS One:

INTRODUCTION

There is evident value in knowing the spatial location of one’s hand; as such knowledge is essential for interacting with our environment. The fact that we position our hand in a spatial context suggests that an external reference frame, fixed to the world, may be important for processing visual and somatosensory signals. The spatial processes that underlie the estimate of hand location appear also to be reflected in movement. For example, the spatial pattern of errors observed with proprioceptive matching is reflected in the pattern of errors in point-to-point movements (Vindras, Desmurget, Prablanc, & Viviani, 1998). Similarly, two groups recently showed a causal link between motor signals and somatosensory systems when motor learning changed the perceived hand position (Ostry et al., 2010; Wong, Wilson, &
Gribble, 2011). It remains unclear how visual, proprioceptive, and tactile modalities come together to create the structure of the hand-location map.

Studies that have probed the interactions between these sensory modalities have given us some important insights. Several studies have demonstrated that tactile feedback helps proprioceptive signals in enhancing end-point accuracy and reducing postural sway (Dickstein, 2005; Helms Tillery, Flanders, & Soechting, 1994; Jeka & Lackner, 1995; Kouzaki & Masani, 2008; Lackner & Dizio, 1994; Lackner, Rabin, & Dizio, 2000; Rabin & Gordon, 2004; Rabin, DiZio, Ventura, & Lackner, 2008; Rao & Gordon, 2001). Likewise, postural signals can clearly affect tactile perception (Azañón, Longo, Soto-Faraco, & Haggard, 2010; Longo & Haggard, 2010a; J. P. Warren, Santello, & Helms Tillery, 2011; S. Yamamoto & Kitazawa, 2001). For example, the spatial interactions between vision and touch have been shown to update with posture of the relevant body part, as long as there is any visual feedback (Azañón & Soto-Faraco, 2007; Botvinick & Cohen, 1998; Kennett, Spence, & Driver, 2002; Maravita, Spence, & Driver, 2003; Spence, 2010; Spence, Pavani, Maravita, & Holmes, 2004). Imaging studies have also shown that proprioception plays a role in tuning and updating this visual-tactile map (Bolognini & Maravita, 2007; Lloyd, Shore, Spence, & Calvert, 2002).

At the level of single neurons, recordings have also shown interactions between the visual, proprioceptive, and tactile modalities. Visual-tactile neurons discharge with tactile stimuli on the hand and visual stimuli near
the same hand, regardless of the position of the hand in space (Fogassi et al., 1992; Gentilucci, Scandolara, Pigarev, & Rizzolatti, 1983; Graziano & Gross, 1997; 1998). More recently, single units in somatosensory cortex have been shown to encode information about both contact with objects as well as movement-related signals (Rincon-Gonzalez, Warren, Meller, & Helms Tillery, 2011b). Although it is believed that the body schema used to adjust posture and guide movement relies on both proprioception and vision (Balslev, 2004; Balslev, Miall, & Cole, 2007; Graziano, 2000; Helms Tillery et al., 1991; Rossetti, Desmurget, & Prablanc, 1995), estimation of hand location appears to rely on proprioception as the fundamental signal, with tactile and visual signals acting to fine-tune this estimation.

Multiple investigators have examined the ability of subjects to identify the spatial location of their hand based on these signals (Adamo & Martin, 2008; Adamovich, Berkinblit, Fookson, & Poizner, 1998; Bagesteiro, Sarlegna, & Sainburg, 2005; L. E. Brown, 2003; L. E. Brown, Rosenbaum, & Sainburg, 2003; Darling & Miller, 1993; Desmurget, Vindras, Grea, Viviani, & Grafton, 2000; Dizio & Lackner, 1995; Goble & Brown, 2007; 2008; Helms Tillery et al., 1991; 1994; Lackner & Dizio, 1994; 2000; Lateiner & Sainburg, 2003; Rao & Gordon, 2001; Smeets, van den Dobbelsteen, de Grave, van Beers, & Brenner, 2006; van Beers et al., 1998; van Beers, Sittig, & Denier van der Gon, 1996; Vindras et al., 1998; Wann & Ibrahim, 1992). Despite this, relatively little is known about the resulting spatial structure of the estimation errors. Constructing and analyzing the spatial pattern of error vectors as subjects estimate the location of their hand has proven difficult. In
particular, the spatial errors for individual subjects in these tasks are frequently large and so idiosyncratic that it is tempting to draw a conclusion that the analyses have not really captured information about spatial representations *per se* (Helms Tillery et al., 1994). Instead, one might conclude that the complex patterns of errors observed in previous studies were the result of overfitting noisy data sets. In fact, these noisy errors have even been explicitly discarded as unexplained drift and variability during data analysis in a few cases (see e.g. (van Beers et al., 1998; van den Dobbelsteen, 2004)).

The spatial structure of the estimation errors of individual subjects has not, to our knowledge, been analyzed in detail. Nonetheless, several studies have made casual observations that the estimation errors appear to be remarkably stable, although subject-specific (L. E. Brown, 2003; L. E. Brown et al., 2003; Desmurget et al., 2000; Helms Tillery et al., 1994; Smeets et al., 2006; van Beers et al., 1996; 1998; Vindras et al., 1998; Wann & Ibrahim, 1992). Despite these repeated observations, analysis of the error patterns in these tasks still tends to focus on generalized effects across subjects. Here we ask whether the patterns truly are subject-specific. If so, this would imply that there is not a single, ideal, proprioceptive map that is acquired by all subjects. Instead, each individual may arrive at a different proprioceptive map based on a unique combination of learning and calibration processes. This would suggest further that many different proprioceptive maps are consistent with accurate and reliable hand position estimation. Consistent with the idea of a calibration of proprioceptive inputs
against visual estimates of hand position, other studies have shown that on average, subject estimations are non-uniform across the workspace. That is, errors are smallest when targets are located closer to the body, near the midline, where subjects have the most experience interacting with objects (Fuentes & Bastian, 2010; Graziano, Cooke, Taylor, & Moore, 2004; Helms Tillery et al., 1994; van Beers et al., 1998; van Beers, Wolpert, & Haggard, 2002; Wilson et al., 2010).

We hypothesize here that we estimate the location of our hands in space using an underlying proprioceptive map that is systematic and stable, but subject-specific. In the present study, we report experiments designed to investigate the individual spatial structure of the proprioceptive map. Specifically, we examined the estimation errors across a 2D horizontal workspace that resulted as subjects used visual, proprioceptive, and/or tactile signals to estimate hand location. Performance was tested at 100 target locations across the workspace by having subjects transform solely proprioceptive information about the position of their hands at a target to a solely visual estimate of the same target. We reconstructed and analyzed the individual spatial structure of the resulting estimation errors under four conditions: tactile stimulation, no tactile stimulation, right hand, and left hand. We found that this structure was stable across conditions and time, but unique to each subject.
MATERIALS AND METHODS

Seven males and two female subjects between the ages of 20 and 35 participated in two different series of experiments. All subjects were free of upper limb neuromuscular impairment and had normal or corrected-to-normal vision. Six subjects were right handed with the following scores 62.5, 76.5, 78.9, 78.9, 80, and 87.5 in the Edinburgh handedness inventory. Three subjects were left handed with scores of -33.3, -73.3, and -100 according to the Edinburgh handedness inventory. All of the subjects signed written informed consent documents before each experiment. This study was approved by the Institutional Review Board at Arizona State University.

Experimental Setup and Procedures. The core task in these experiments was estimation of the 2D location of the index fingertip after it was passively displaced to a target and taken back to the resting position. In order for the subjects to report their estimated hand location without subsequent movement of either arm, we created a 2D grid with labeled locations so that subjects could verbally report fingertip location (Figure 2.1A). The grid was marked with A through K rows and 1 through 14 columns. Each square on the grid was 5 by 5 cm and had four colored targets, which were 0.4 cm in diameter. There were a total of 616 targets located 1.25 cm apart along the horizontal (x) and depth (y) dimensions.
Figure 2.1. Experimental setup. (A) Each square was labeled with a row letter, a column number, and four colored circles (red, yellow, green, and blue). (B) The colored targets represent an example of a target set. The superimposed vector field represents an example of a spatial structure of mean errors generated with the fourth-order regression. The beginning of the arrow indicates the target where the finger was positioned and the arrowhead indicates where the subject’s estimation of the target.

Subjects sat 15 cm in front of the grid, which was set on a stationary and horizontal table. Each subject was asked to align the body’s midline with the grid’s midline, which was located between columns 7 and 8. Both hands initially rested on the chair’s armrests (resting position), located 2 cm from the edge of the grid. On each trial, the experimenter grasped the subject’s wrist, being careful not to touch the hand, and passively moved it to a target where one of two conditions (see below) was applied for about 5 sec. Subjects
were asked to keep their eyes closed and their index finger extended during each movement. After the hand was passively brought back to the resting position, the subject was asked to look at the grid and verbally report the grid location where they thought their index finger had been located, without making a reaching movement. Subjects used the column letters, row numbers, and target colors to identify the estimated location (e.g. d5y), and never received feedback regarding the actual location of the target. All of the trials were performed by the same experimenter, who strove to keep the passive displacement constant and without significant change between trials and conditions. No specific path or trajectory was used to move the finger to and from the target. This process was repeated for 100 different targets for each condition and hand. The 100 targets were chosen to be evenly distributed on the grid: an example target set is shown in Figure 2.1B. The target distribution was varied slightly among subjects to account for differences in arm lengths and depended on which row subjects could reach without moving the torso. There were three different target sets, A, B, C, in which the targets were evenly distributed up to either rows K, J, or I, respectively (see Table 2.2 for target set assignment). The same target set was used in the same order for the same subject in the Touch and No-Touch conditions and was reflected across the midline for the other hand. Subjects were able to reach any target within the workspace. In all cases, the targets were evenly distributed across the midline.

The order of the stimulation conditions was randomly assigned to subjects as they were recruited. The right hand was completed first for all
subjects in one block of experiments, and then the same subjects were re-recruited 4 months later to repeat the experiment with their left hand. Each stimulation condition was completed on a separate day.

In the Touch condition the subject received tactile stimulation: the experimenter lightly pressed the subject’s fingerpad to a target on the grid and held it there for 5 seconds. In the No-Touch condition the subjects did not receive tactile stimulation. The experimenter held the wrist with the subject’s index finger about 2 cm above the target surface for 5 seconds. Although this procedure was not standardized, it was not changed from trial to trial or from experiment to experiment.

**Analysis.** Performance was evaluated by measuring the direction and magnitude of the errors between the actual and estimated target locations (Figure 2.2). More specifically, the x and y coordinates of the actual and estimated location of each target were measured and used to calculate error vectors, which in turn were used as estimates of the spatial structure of the proprioceptive map.

We first quantified the degree of similarity between patterns of errors exhibited in different conditions and between subjects. To this end, we used a vector field correlation method for quantifying the effect of subjects, tactile feedback and hand used on the vector field shape and scale (Buneo, 2011). Briefly, this nonparametric method describes the degree of relatedness between two sets of two-dimensional vectors by producing a correlation coefficient, $\rho$, that is analogous to a scalar correlation coefficient. It also
takes into account irregularities and asymmetries in the fields to quantify the
degree of rotational or reflectional dependence and the scaling relationship
between the vector fields. The correlation coefficient ranges from -1 to 1,
which represents a perfect reflectional relationship and a perfect rotational
relationship, respectively. This method also provides the angle of rotation
that best aligns the vector fields, $\theta$, and a scale factor, $\beta$, that describes the
scaling relationship between the two fields. Correlating a field with itself
would result in a $\rho$ of 1, a $\theta$ of 0°, and a $\beta$ of 1. We used this method to
analyze the relationship between two patterns of errors by comparing two
vector fields at a time. Note that for comparisons between hands the
constant error vector field from one hand was reflected and then
superimposed on the error vector field from the other hand. Lastly, as a
control analysis, we also performed the correlation after shuffling the vectors
in one vector field and pairing them with the vectors in the other field.

The direction of the error vectors was analyzed to determine if the
spatial structure of the estimation errors differed significantly between
hands, stimulation conditions, and subjects. In order to analyze differences
in the spatial structure of the estimation errors between hands, the constant
error vector field from one hand was reflected and then superimposed on the
error vector field from the other hand for the same condition (see e.g. Figure
2.3). Then, the absolute angular difference between each of the superimposed
vectors was measured. We used the same method, without the reflections, to
analyze differences in the spatial structure of the estimation error between
stimulation conditions (Touch/No-Touch) for each hand. As a control, the
vectors in one of the error vector fields were shuffled and spatially randomized before being superimposed onto the other error vector field. This randomization provided a “null” distribution, which accounted for any overall biases in the pattern of errors for a given subject. The distributions of the two different sets of angles were plotted and analyzed by the Kolmogorov-Smirnov (K-S) test.

The K-S test measures whether two cumulative distributions are different from each other by finding the greatest difference between the two and assigning it a k-value and a p-value (see e.g. Figure 2.3). A large k-value and a p-value of less than .05 indicate that the two angle distributions (unshuffled vs. shuffled) are significantly different and that the two vector fields are significantly more similar than would be expected by chance. This provided a measure for the stability of the structure of the estimation errors within-subjects for the four experimental conditions. On the other hand, a non-significant difference in distributions indicates that the two vector fields can be described as no more similar than would be expected by chance (see Figures 2.4 and 2.5). This provided a measure for the idiosyncrasy of the performance when comparing the spatial structure of the estimation errors between-subjects. Since there were three different target sets, only those target locations that matched across subjects were used for the K-S test and vector correlation analysis.

In addition to analyzing the direction of the errors, we looked at the accuracy of the performance: we used ANOVA to statistically analyze the
magnitudes of the errors. The mixed model had four main factors at different levels and one interaction factor: stimulation (Touch vs. No-Touch), dominance (right-handed vs. left-handed), hand (right hand vs. left hand), subjects (1-9) treated as random variables, and interaction between stimulation and hand. The response in the model consisted of one mean error per factor; each mean error resulted from averaging the 100 errors in each experimental condition. The Tukey’s HSD (Honesty Significant Difference) posthoc test was used to test the differences among the least square means (LSmeans) at a significance level of 0.05. JMP software (SAS, Cary, NC, USA) was used to run the model.

Finally, to investigate how the accuracy of performance varied across the workspace, we measured the magnitude of the errors at six different segments in the grid. Lateral location of the targets: left hemifield \((x = 0-25 \text{ cm})\), middle \((x = 25-45 \text{ cm})\), right hemifield \((x = 45-70 \text{ cm})\), and distance from body: near field \((y = 0-25 \text{ cm})\), and far field \((y = 25-50 \text{ cm})\). This measure was similar to the configuration adopted by Wilson et al. (2010), where proprioceptive bias and acuity was tested at 9 positions for both hands: near, middle, far, left, center, and right (Wilson et al., 2010). In contrast with their design, subjects in the current study performed the experiment with both hands so it seemed appropriate to test the effect of ipsilateral and contralateral fields. Specifically, we wanted to examine how subjects’ accuracy varied between targets that were located closer and farther away from the body and if there was an effect of crossing the midline. As for the analysis described above, we built an ANOVA model to examine these effects.
The response in the model consisted of six mean errors per effect: each mean error resulted from averaging all the errors in each of the six segments. The mixed model had six main effects and two interactions. The main effects were: stimulation (Touch vs. No-Touch), dominance (right-handed vs. left-handed), hand (right hand vs. left hand), subjects (1-9) treated as a random variable, lateral location (ipsilateral: right hand in right hemifield and left hand in left hemifield, middle, and contralateral: right hand in left hemifield and left hand in right hemifield), distance from body (near vs. far fields), and interaction between stimulation and hand and also between lateral location and distance from body.

A stepwise regression was used on a 4th order polynomial to build a model of the raw data, which allowed us to estimate consistent errors made by the subjects and to smooth the data for visualization purposes. These errors are referred as ‘constant errors’ throughout the manuscript. Equations were created for each experiment and only contained those parameters that contributed significantly to the fit. This method allowed us to capture spatial regularities in each subject’s performance without requiring repeated measures. The model was used to plot the spatial organization of the error vectors by using 48 locations evenly distributed over the target space and contained entirely within the sampled workspace (Figures 2.1B, 2.2 and 2.3). All statistical analyses were performed on both the errors calculated from the raw data and the constant errors obtained from the 4th order regression.
RESULTS

To investigate the structure of the proprioceptive map used to estimate hand location, subjects were tested across a 2D horizontal grid at 100 target locations. The resulting spatial pattern of estimation errors was analyzed for the right and left hands in the No-Touch and Touch conditions.

Spatial Structure. Figure 2.2 shows the constant errors made by six right-handed and two left-handed subjects for the right hand with tactile feedback. Each of the eight panels represents a complete grid with the midline at 35cm. Subjects aligned themselves with this midline as shown in the bottom right panel. Each constant error is represented with an arrow indicating magnitude and direction. The beginning of the arrow indicates the target where the finger was positioned by the experimenter, and the arrowhead indicates the subject’s estimation of that finger position, as predicted by the fourth-order regression. Note the differences between subjects. Each subject appeared to exhibit a spatial pattern of errors that was distinct from that of the other subjects'. For example, all subjects appeared to have points of minimum error that were located in a different workspace location.
Figure 2.2. Similarity of pattern of errors across subjects. Distribution of errors from six right-handed and two left-handed subjects when using the Right hand in the Touch condition. Each arrow represents the constant error predicted by the fourth-order regression. The human figure represents the location of a subject with respect to the grid and the resulting pattern of errors. The text in the middle of the figure represents the resulting values from the K-S test and vector correlation analysis for the comparison between the adjacent (above and below) two vector fields.

Although the patterns of errors across subjects appeared idiosyncratic, there was a striking similarity between hands and Touch/No-Touch conditions for each subject. Figure 2.3 shows the constant errors made by one left-handed subject at each target location for both hands and tactile stimulation conditions. Note the similarities between the Touch and No-Touch conditions and the near mirror-image symmetry between hands. This
subject tended to undershoot faraway targets, resulting in a spatial pattern of errors that points towards the body and contralateral arm.

**Figure 2.3.** Similarity of pattern of errors across hands and conditions.

Distribution of errors from one left-handed subject for both hands and both tactile feedback conditions. Same format as in Figure 2.2. The text in the right bottom corner represents the resulting values from the K-S test and vector correlation analysis for each of the comparisons in the figure.

We used the vector field correlation method to quantify the similarity between hands and conditions. Table 2.1 shows the mean and standard deviation of the unsigned values of ρ, θ, and β, for each comparison. For θ,
circular statistics were used to obtain these values (Berens, 2009). First, we compared the Touch and No-Touch vector fields for both the right and left hands. The correlation coefficients obtained in most of the individual comparisons were positive, indicating a rotational rather than a reflectional relationship generally existed between the fields. More importantly the mean correlation coefficients and the angles of reflection/rotation showed that tactile feedback did not change the overall structure. That is, on average the vector fields in the two stimulation conditions were highly correlated ($\rho = 0.82$) with a small angle ($\theta = 22.00$) and a scaling factor close to 1 ($\beta = 0.91$). This was especially true when compared to the correlation coefficient, angle, and scaling factor obtained when the vectors in each field were shuffled (Table 2.1). Interestingly, the vector fields were more highly correlated between stimulation conditions for the right hand ($\rho = 0.86$, $\theta = 20.67$, $\beta = 1.04$) than for the left hand ($\rho = 0.79$, $\theta = 23.46$, $\beta = 0.77$).
Table 2.1

Test of Similarity Across Hands, Conditions, and Subjects: Resulting ρ, θ, β from The Vector Field Correlation Analysis of The Raw and Constant Errors.

<table>
<thead>
<tr>
<th></th>
<th>Constant Errors</th>
<th>Raw Errors</th>
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<tr>
<td></td>
<td>Between Hands</td>
<td>Between Tactile Conditions</td>
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<tr>
<td></td>
<td>M ρ</td>
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<td>18.48</td>
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<td>.12</td>
<td>11.34</td>
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<td></td>
<td>.10</td>
<td>26.4</td>
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Note. M=Mean. SD=Standard Deviation. θ angles in degrees.


Next we compared the error patterns between the hands within a given stimulation condition. Here again, the individual comparisons generally resulted in positive correlation coefficients. On average, we found that the vector fields were quite similar for this comparison (ρ = 0.69, θ = 22.92, β = 0.83). Note that prior to correlating the fields between hands we first
reflected the error vector field from one hand and superimposed it on the error vector field from the other hand. Thus, the relatively high degree of similarity between the fields suggests an approximately mirror image relationship existed between the vector fields for the two hands.

In order to further examine these effects, we calculated the distribution of the angles between error vectors that resulted from superimposing the error vector field from one condition onto those from the other condition. When comparing between hands, we took the mirror image of the error vector field from the left hand and superimposed it onto the error vector field from the right hand. As a null condition, we also measured the distribution of angles resulting when the error vectors from one vector field were shuffled and randomly paired to the error vectors of the other vector field (see Methods). This took into account the fact that the general distribution of errors for many subjects was nonuniform (e.g. subject CP in Figure 2.2 had a distribution of errors all pointing away from the subject, thus the distribution of angles between two separate conditions could be very nonuniform based merely on that bias). Our null hypothesis was that the two angle distributions (unshuffled vs. shuffled) came from the same distribution, and the alternative hypothesis was that the two angle distributions were from different distributions. Therefore, rejecting the null hypothesis meant that the two vector fields were significantly more similar than would be expected by chance.
Figure 2.4 shows representative histograms of the angles formed between the superimposed error vectors from both hands for the subject shown in Figure 2.3. The top histograms correspond to the No-Touch condition and the bottom histograms correspond to the Touch condition. The panels on the left show the angle distribution of the superimposed error vectors from both hands. The panels on the right show the angle distribution of the superimposed vectors when the error vectors from one hand were shuffled before being superimposed. This subject had a higher frequency of smaller angles formed by the unshuffled vectors, indicating that the distribution of errors for both hands was very similar between hands for both conditions. In contrast, the angle distributions created by the shuffled vectors have smaller peaks and look more spread than the histograms on the left. Therefore, the spatial structure of estimation errors created by one hand was similar to the spatial structure of estimation errors created by the other hand. In addition, the same effect was observed when measuring the similarity of the error distributions between stimulation conditions (data not shown).
Figure 2.4. Histograms of the angles between the superimposed vectors. The left histograms show the angle distribution of the superimposed constant error vectors across hands for the subject displayed in Figure 2.3. The right histograms show the angle distribution of the superimposed vectors when the constant errors from one hand were shuffled before being superimposed.

To verify this effect, we compared the angle distributions using a Kolmogorov-Smirnov (K-S) test. Figure 2.5 shows the average cumulative distribution of the angles from all nine subjects obtained from the superimposed error vectors. The top two panels show the unshuffled and shuffled distributions that resulted from comparing the vector fields between hands for the No-Touch and Touch conditions. Similarly, the bottom two
panels show the distributions that resulted from overlaying and comparing the vector fields across conditions for the Left and Right hands. The k-value represents the greatest distance between the two distributions and is used for the K-S test, which measures whether two distributions are significantly different from each other. The top trace (blue circles) in each panel represents the cumulative distribution of the unshuffled error vectors and the bottom trace (red triangles) represents the cumulative distribution of the shuffled error vectors.

Figure 2.5. Average cumulative distribution of angles. The distributions contain the pooled data from all nine subjects for the angles obtained from
the superimposed constant error vectors for both hands and conditions. The k-value represents the greatest distance between the two distributions.

The average distribution of the unshuffled error vectors shows a higher frequency of smaller angles than the distribution of the shuffled error vectors since the cumulative distribution of the former rises faster than the cumulative distribution of the latter. Table 2.2 shows the results of the K-S test on the raw data and constant errors (between parentheses) from the regressions for each subject when comparing the spatial structure of the estimation errors between hands and conditions. The resulting angle distributions from the unshuffled and shuffled constant and raw error vector fields between hands were significantly different in most instances. Specifically, the spatial structure of constant estimation errors of all but 4 comparisons was significantly more similar between hands and conditions than would be expected by chance. Similarly, the spatial structure of raw estimation errors of all but 2 comparisons was significantly more similar between hands and conditions than would be expected by chance. In addition, the spatial structure had a significant degree of similarity between hands, which suggests an approximately mirror image relationship existed between the vector fields for the two hands. Since these measures were separated by four months, this also tells us that the structure was stable across time.
Table 2.2

Test of Similarity Across Hands and Conditions: Resulting k and p-values from The K-S Test

<table>
<thead>
<tr>
<th>Subject</th>
<th>Right-Left Hands</th>
<th>No Touch-Touch</th>
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<tbody>
<tr>
<td></td>
<td>k</td>
<td>p</td>
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<tr>
<td>DM (A)</td>
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<td></td>
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<tr>
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<tr>
<td></td>
<td>(.188)</td>
<td>(.333)</td>
</tr>
<tr>
<td>IK (A)</td>
<td>.329**</td>
<td>1.3E-04</td>
</tr>
<tr>
<td></td>
<td>(.583**)</td>
<td>(6.2E-8)</td>
</tr>
<tr>
<td>JL (C)</td>
<td>.366**</td>
<td>2.1E-05</td>
</tr>
<tr>
<td></td>
<td>(.354*)</td>
<td>(.003)</td>
</tr>
<tr>
<td>LF (A)</td>
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<td>.003</td>
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<tr>
<td></td>
<td>(.458**)</td>
<td>(4.6E-5)</td>
</tr>
<tr>
<td>MB (C)</td>
<td>.213*</td>
<td>.032</td>
</tr>
<tr>
<td></td>
<td>(2.92*)</td>
<td>(.027)</td>
</tr>
<tr>
<td>NB (A)</td>
<td>.316**</td>
<td>7.5E-05</td>
</tr>
<tr>
<td></td>
<td>(.521**)</td>
<td>(2.1E-6)</td>
</tr>
<tr>
<td>CP (B)</td>
<td>.369**</td>
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<td>(6.2E-8)</td>
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<tr>
<td>TS (B)</td>
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<td>.644</td>
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<td>(.333)</td>
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In addition to measuring the similarity between hands and stimulation conditions, we also quantified the idiosyncrasy of the spatial structure of the estimation errors. This was done by comparing the distribution of angles formed when the error vector field for one hand and one condition from one subject was superimposed onto the error vector field for the same hand and condition from another subject. Only the error vector fields for one condition and one hand were paired at a time and each subject was compared to every other subject separately, resulting in 144 comparisons. As explained above, failure to reject the null hypothesis meant that the vector fields from the two subjects being compared were no more similar than would be expected by chance, and were thus idiosyncratic.

Tables 3 and 4 show the results of the K-S test when comparing the spatial structure of the estimation (raw and constant) errors between subjects for all conditions, and for left (Table 2.3) and right (Table 2.4) hands. Table 2.3 shows the results of the K-S test when subjects used the Left hand. The \( p \)-values above the diagonal come from the K-S test between subjects for the
Left hand and Touch condition, while the p-values below the diagonal come from the K-S test between subjects for the Left hand and No-Touch condition. Similarly, Table 2.4 shows the two sets of p-values for each pair of subjects compared when they used the Right hand with and without tactile feedback. Out of the 144 comparisons, only 3 (2%) comparisons exhibited a non-idiosyncratic distribution of raw errors, and only 14 (9.7%) comparisons exhibited a non-idiosyncratic distribution of constant errors. The overall spatial structure of the estimation errors was significantly no more similar than would be expected by chance. In other words, the spatial structure of subjects’ estimation errors was idiosyncratic.
Table 2.3

*Test of Similarity Between Subjects for the Left Hand: Resulting p-values from the K-S Test*

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Note. S=Subjects. LH=Left Hand. T=Touch Condition. NT=No Touch Condition. Numbers enclosed in parenthesis represent the resulting p-values from the analysis on the constant errors. While the other numbers represent the analysis on the raw errors. Adapted from “The Proprioceptive Map of the Arm Is Systematic and Stable, but Idiosyncratic,” by L. Rincon-Gonzalez et al. 2011, PLoS ONE, 6, e25214.
* $p < .05$. **$p < .01$
Table 2.4

Test of Similarity Between Subjects for the Right hand: Resulting p-values from the K-S test

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Note. S=Subjects. RH=Right Hand. T=Touch Condition. NT=No Touch Condition. Numbers enclosed in parenthesis represent the resulting p-values from the analysis on the constant errors. While the other numbers represent the analysis on the raw errors. Adapted from “The Proprioceptive Map of the Arm Is Systematic and Stable, but Idiosyncratic,” by L. Rincon-Gonzalez et al. 2011, PLoS ONE, 6, e25214.

* $p < .05$. **$p < .01$

The vector field correlation analysis also supports this conclusion. Table 2.1 shows that on average the vector fields were less strongly correlated between subjects than between conditions and hands for the same subject. Similarly, the scaling factor was smaller (farther from 1) between the vector fields of two subjects than within one subject. In general, comparisons across subjects were better correlated for the Right hand and Touch condition than any other condition (Right hand, T: $\rho = 0.70$, $\theta = 47.41$, $\beta = 0.75$; Left hand, T: $\rho = 0.65$, $\theta = 31.81$, $\beta = 0.69$; Right hand, NT: $\rho = 0.60$, $\theta = 41.19$, $\beta = 0.62$; Left hand, NT: $\rho = 0.63$, $\theta = 34.93$, $\beta = 0.72$). In these set of comparisons, we observed 76 negative correlation coefficients for the constant errors and 52 for the raw errors.

**Magnitude of The Error.** We measured the mean errors made by each subject in order to verify whether the Touch condition had an effect on reducing the magnitude of the errors and thus on accuracy. We also measured the effect of using either hand on improving accuracy. Table 2.5 shows the results from the fixed factor ANOVA, which resulted in a mean error of 5.49 cm, an $R^2$ of 0.73 and an $R^2$-adjusted of 0.69. Only the effects of
stimulation, and the interaction of stimulation and hand (Stim X H) were significant. The mean error was significantly lower in the Touch (5.21 cm) condition than in the No-Touch (5.78 cm) condition. However, hand used, hand dominance, and interactions with hand dominance had no effects in the model and had no significant interactions with the other factors. On the other hand, the post-hoc test on the stimulation and hand interaction effect revealed that when subjects used their right hand, the tactile condition was statistically more accurate than when using the right hand with no tactile feedback; this difference did not exist for the left hand. (Post-hoc Stats: \( p < .05 \), LSmean (T, R) = 5.02*, LSmean (N, R) = 6.14*, LSmean (T, L) = 5.40, LSmean (NT, L) = 5.42, std error = 0.32).

Table 2.5

<table>
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<th>df</th>
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<th>( p )</th>
</tr>
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<td>.02</td>
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<tr>
<td>Hand (H)</td>
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<td>0.17</td>
<td>.69</td>
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<td>Dominance (D)</td>
<td>1</td>
<td>0.01</td>
<td>.96</td>
</tr>
<tr>
<td>Stim X H</td>
<td>1</td>
<td>6.10*</td>
<td>.03</td>
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</table>

*Note. Adapted from “The Proprioceptive Map of the Arm Is Systematic and Stable, but Idiosyncratic,” by L. Rincon-Gonzalez et al. 2011, PLoS ONE, 6, e25214. * \( p < .05 \). ** \( p < .01 \)

Finally, to investigate how accuracy of estimating hand location varied across the workspace, we measured the magnitude of the estimation errors at six different segments in the grid. Specifically, we wanted to examine
whether distance from the body or lateral target location on the workspace had an effect on accuracy. Table 2.6 shows the results of the fixed factor ANOVA on the divided grid, which resulted in an $R^2$ of 0.55 and an $R^2$-adjusted of 0.53.

Table 2.6

*Analysis of Variance for the Uniformity of the Accuracy Across the Workspace*

<table>
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<td>.24</td>
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<td>Distance from Body (DB)</td>
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<td>&lt;.0001</td>
</tr>
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<td>1</td>
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<td>LL X DB</td>
<td>2</td>
<td>4.96**</td>
<td>&lt;.01</td>
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* $p < .05$. ** $p < .01$

As observed with the pooled vectors in the workspace, the ANOVA on the divided grid revealed significant effects of stimulation conditions, target location on the grid, and the interaction of stimulation and hand as well as the interaction of lateral location and distance from the body factors (Table 2.6). Regarding the main effect of stimulation conditions and its interaction
with the hand used, we observed the same effect as described above. (Post-hoc Stats: $p < .05$, LSmean (T, R) = 4.99*, LSmean (N, R) = 6.19*, LSmean (T, L) = 5.45, LSmean (NT, L) = 5.48, std error = 0.28).

We found that the magnitude of the estimation errors was not uniform across the workspace for all subjects. When analyzing the distance from the body effect (Near: all x’s and y = 0-25 cm; Far: all x’s and y = 25-50 cm), subjects were more accurate at estimating targets that were located closer to their bodies ($p < .0001$, LSmean (Near) = 4.71, LSmean (Far) = 6.35, std error = 0.26). When analyzing the lateral location of the targets effect (left hemifield: all y’s and x = 0-25 cm; middle: all y’s and x = 25-45 cm; right hemifield: all y’s and x = 45-70 cm), the performance at the middle location was significantly different than at the contralateral location (LSmean (Middle) = 5.23*, LSmean (Ipsi) = 5.48, LSmean (Contra) = 5.88*, std error = 0.27). Subjects were most accurate at estimating hand location at targets located directly in front of their bodies (middle of the grid).

In addition, the interaction between the lateral location of targets and distance from the body (grid divided into 6 segments) was significant (LSmean (Ipsi, Near) = 4.33, LSmean (Middle, Near) = 4.47, LSmean (Contra, Near) = 5.31, LSmean (Middle, Far) = 5.98, LSmean (Contra, Far) = 6.44, LSmean (Ipsi, Far) = 6.63, std error = 0.30). Figure 2.6 shows the interaction effect in which subjects were more accurate at estimating hand location when the targets were near the body and in the ipsilateral near field. Crossing the midline resulted in significantly less accurate estimations when in the near
This effect of crossing the midline was not significant when the targets were located farther away from the body.

**Figure 2.6.** Proprioceptive accuracy as a function of lateral location and distance from the body. Analysis of variance of the average error magnitude at 6 different locations on the grid. Lateral location of the targets: Ipsilateral (x = 0-30 cm), Middle (x = 30-40 cm), Contralateral (x = 40-70 cm), and distance from body: Near field (y = 0-25 cm), and Far field (x = 25-50 cm). LSMeans Differences Tukey HSD posthoc test on the significant interaction between lateral location of targets and distance from the body revealed significant interactions between different locations on the grid. Interactions found between the dotted lines are not significant at a \( p < .05 \). Everything else is significantly different.

**DISCUSSION**

In this study we investigated the proprioceptive map of arm position information by reconstructing and analyzing the individual spatial structure of endpoint estimation errors under four conditions: with and without tactile
feedback, and with the right and left hands. We also examined the dependence of the results on handedness. We found that tactile feedback improved subjects’ ability to accurately estimate hand location but did not affect the directional pattern of the errors. While we observed that the effect of tactile feedback was limited to the right hand, handedness had no effect on subjects’ accuracy. We also found that the spatial structure of the direction of the errors was stable across conditions and time. Furthermore, we showed statistically that the spatial structure of the estimation errors was idiosyncratic: each subject had a unique spatial structure of estimation errors. Finally, as has been previously shown, we found that the magnitude of the errors had a characteristic and non-uniform distribution over the workspace: errors were smallest close to the body and closer to the body midline. We argue here that these observations are consistent with a proprioceptive map that is constructed by experience using one systematic and stable but idiosyncratic algorithm that is constantly being recalibrated against visual signals.

Although tactile input did not alter the overall structure of the proprioceptive map as seen in the significantly similar fields in the K-S test and highly correlated vector fields, we did find, in agreement with previous studies, that tactile feedback improved the accuracy of hand location estimates (Dickstein, 2005; Helms Tillery et al., 1994; Jeka & Lackner, 1995; Kouzaki & Masani, 2008; Lackner et al., 2000; Lackner & Dizio, 1994; Rabin et al., 2008; Rabin & Gordon, 2004; Rao & Gordon, 2001; Vindras et al., 1998). We found this to be a significant effect whether we looked at the

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errors across the entire workspace, or when the errors were examined separately for 6 different segments of the workspace. In addition, both ANOVA tests showed that when subjects used their right hand, the tactile condition was statistically more accurate than the no tactile stimulation condition; this difference neither existed for the left hand nor depended on handedness. In agreement with the ANOVA result, the vector fields were shown to be better correlated between subjects in the right hand and Touch condition and within subjects across stimulation conditions for the right hand. These results are contrary to what we expected based on previous studies (Bagesteiro, 2002; Duff & Sainburg, 2006; Goble & Brown, 2007; 2008; Goble, Lewis, & Brown, 2006; Goble, Noble, & Brown, 2009; Sainburg, 2005; Sainburg & Kalakanis, 2000; Schaefer, Haaland, & Sainburg, 2009; Wang & Sainburg, 2007), which have shown that the nondominant system is better at controlling limb position. On the other hand, Wilson et al. (2010) reported better acuity for the right arm in a proprioceptive matching task (Wilson et al., 2010). The heterogeneity of these findings in the literature is likely due to the differences in experimental procedures. The studies by Goble and colleagues used proprioceptive target matching tasks, while the studies by Sainburg and colleagues used reaching movement tasks, and the current study used a proprioceptive to visual transformation of target location. In any case, our results do not imply that touch perception is independent from proprioception: touch appears to be body-referenced and moves with the body (e.g. tactile perception depends on hand posture,
Our key observation is that the spatial structure of the estimation errors is stable across multiple measurements. First, it is symmetric between the hands. That is, the errors made with the right hand looked like an approximate mirror image of the errors made with the left hand, irrespective of the tactile conditions. Here, when we compared the vector field from one hand with a reflected version of the vector field from the other hand we found that the two fields were well correlated. We also showed statistically that the spatial structure of estimation errors was more similar between hands than would be expected by chance. This finding agrees with previous observations that hand biases were mirror-symmetric, which suggested that subjects represent their limbs in space by two separate frames of reference originating at each shoulder (Haggard, Newman, Blundell, & Andrew, 2000; Jola, Davis, & Haggard, 2011). Thus, even though each arm operates in its own egocentric space, it appears that the computations based on the posture of the arms use one algorithm to build the spatial map. The fact that the two arms exhibit mirror-image patterns suggests that this egocentric space is anchored at the shoulder and that this idiosyncratic computation is performed in the same way for each arm. Recent work from Fuentes and Bastian (2010) suggests which variables are important for this computation: proprioceptive biases are dependent on joint configuration and are independent of the task (Fuentes & Bastian, 2010). Finally, the spatial structure of this map is stable not just across tasks, but over time. That is,
the spatial structure of the estimation error was not substantially affected when subjects were re-recruited 4 months after the initial set of experiments. Thus, there is one systematic and stable solution to building the proprioceptive map of hand location.

The fact that the spatial structure of the estimation errors was significantly different across subjects suggests that each individual’s map is uniquely constructed through a learning mechanism and is thus the result of individual experience. This is in agreement with previous reports: in an endpoint position matching task, dancers showed better integration of proprioceptive signals and also relied more on proprioceptive signals than visual signals compared to non-dancers (Jola et al., 2011); in a bimanual parallellity task, what subjects haptically perceived as parallel was influenced by job experience or education (Kappers, 2003). In addition, our results statistically validate casual observations in the literature that the pattern of errors is subject specific (L. E. Brown, 2003; Desmurget et al., 2000; Helms Tillery et al., 1994; Kappers, 2003; Smeets et al., 2006; van Beers et al., 1996; 1998; Vindras et al., 1998). The repeatability of these patterns across conditions and time shows that the patterns are not statistical anomalies resulting from overfitting of noisy data. Rather, the idiosyncrasy is a fundamental byproduct of how proprioceptive information is processed. Both the idiosyncrasy and common features in the spatial structure can be seen in the vector correlation analysis across subjects as the vector fields between subjects were less correlated than the vector fields within subjects, yet, more correlated than the control condition.
While we have focused on the idiosyncrasy, our results do not contradict prior results showing overall patterns in pooled data. In fact, the overall distribution of error magnitudes, as shown when we divided the grid into 6 spaces, is comparable to that shown by Wilson et al. (2010) where proprioceptive bias and acuity was tested at 9 positions for both hands (Wilson et al., 2010). In agreement with this study and another study by van Beers et al. (1998) (van Beers et al., 1998), we found that all subjects were more accurate at estimating the location of their hands when the targets were closer to the body.

These observations on the structure of the pooled map suggest that the spatial structure of the estimation errors is a consequence of a system that is continually calibrating the proprioceptive map of hand location against the visual representation. The area where we have the most experience interacting with objects (close to the body, near the midline) is where the calibration appears best, and the calibration decreases as you go away from that location. The fact that the idiosyncrasy in the pattern of errors exists for locations close to the body, where the system is highly calibrated across subjects, suggests that the map is based on a general mechanism for estimating hand location given arm configuration: the larger errors at the periphery shape the entire pattern of errors, instead of being limited to the periphery which one might expect in the case of a set of local solutions. Based on these ideas, local perturbations to the structure of the map should propagate throughout the map just like the idiosyncrasy of the errors.
The results presented here provide insight into the structure of the proprioceptive map of the arm: it is systematic and stable, but idiosyncratic. The stability of estimation errors across conditions and time suggests the brain constructs a proprioceptive map that is reliable, even if it is not necessarily accurate. The idiosyncrasy across subjects emphasizes that each individual constructs a map that is unique to their own experiences. Finally, the commonalities seen across subjects suggest that the system is continually being calibrated against other sensory signals.

Taken together, this study highlights the value of studying individual differences in motor performance. Idiosyncrasies might be crucial in allowing us to understand how the central nervous system constructs and uses this map of arm location. Furthermore, this knowledge could be critical in the design of neuroprosthetic devices capable of somatosensory feedback.
Chapter 3

INTERACTION BETWEEN TACTILE AND PROPRIOCEPTIVE REPRESENTATIONS


INTRODUCTION

We can now decode motor cortical activity, recorded using a variety of multi-channel methods, into a signal that can be viably used to control computer cursors, robotic arms and hands, and neuroprosthetic limbs (Ganguly & Carmena, 2009; L. R. Hochberg et al., 2006; Shenoy et al., 2003; D. M. Taylor, Tillery, & Schwartz, 2002; Velliste, Perel, Spalding, Whitford, & Schwartz, 2008). Yet while the motor aspect of such prosthetics has progressed well in the past decade, the sensory side remains lacking. Somatosensory prostheses remain rudimentary compared to auditory and visual prostheses. Neuroprosthetic hands, for example, regardless of the sophistication of their motor control algorithms are far from providing the kind of sensations that are crucial for manipulating objects and physically interacting with the environment. When grasping an object, the central nervous system extracts object features such as size, texture, and also spatial elements based on hand posture and touch receptors activated by the contact. Technology is just now getting to a point to provide those kinds of sensations (Dhillon & Horch, 2005; Fishel & Loeb, 2012; Kuiken, Marasco, Lock,
Harden, & Dewald, 2007; Marasco, Kim, Colgate, Peshkin, & Kuiken, 2011; O'Doherty et al., 2011; Su, Fishel, Yamamoto, & Loeb, 2012; Wettels, Santos, Johansson, & Loeb, 2008). Moreover, the same sensory signals are used to monitor the status of ongoing manipulations and are thus crucial for normal motor control (Ghez, Gordon, Ghilardi, Christakos, & Cooper, 1990). It follows that to be able to provide natural feedback from an artificial hand to the user of a neuroprosthetic device, it is necessary to provide both tactile and proprioceptive information. However, there is still a lack of understanding of the interaction between internal representations of proprioception and touch. With an overall goal of recreating such sensations, we have been motivated to study this interaction.

Specifically, how do signals in these channels interact in order to form a unified perception of an object? Recent stimulation work has provided evidence that signals in both proprioceptive and cutaneous neural channels are required for stereognosis (Horch, Meek, Taylor, & Hutchinson, 2011). Proprioceptive and tactile signals provided through their respective channels allowed one amputee to discriminate grasped objects, while information about finger position and object compliance provided solely through tactile channels was not enough to allow object discrimination above chance levels for another amputee. Understanding how signals in these two channels are affected by stimuli will be crucial for allowing users of prosthetic devices to identify and manipulate objects.

Despite these clear interactions, proprioceptive and tactile signals are perceived as separate and likely work at different levels of consciousness.
When manipulating an object, we are immediately conscious of contact through tactile receptors: we can distinguish roughness, temperatures, edges, and surface curvature. By contrast, perception of body posture is much less vivid and works at a more subconscious level (Berlucchi & Aglioti, 2010; Carruthers, 2008). Indeed, these signals are not only perceived differently but they might have different cortical representations. It is well known that tactile signals are represented in a somatotopic manner in the somatosensory cortex; however, such representation has not yet been found for proprioception. Nevertheless, several studies on body representations and our sense of embodiment suggest that we have a stable internal representation that encodes the position of our body parts in space and that somatotopic maps interact with such body representations (Berlucchi & Aglioti, 2010; Carruthers, 2008; Longo & Haggard, 2010a; Serino & Haggard, 2010). If proprioception is a critical component of this stable representation and tactile signals interact with it, studying how the internal representations of touch and proprioception interact at both the perceptual and cortical levels would be critical for understanding how to provide sensation in a neuroprosthetic system.

With experiments probing the internal representation of arm location and the somatotopic representation of touch, we addressed how signals in proprioceptive and tactile channels are affected by stimuli that drive primarily the other channel. We have been examining the interrelationships between these two signals at the psychophysical and neurophysiological levels (Rincon-Gonzalez, Buneo, & Helms Tillery, 2011a; Rincon-Gonzalez,
Having previously reconstructed a map of proprioception based on subjects’
perception of arm location in space, we investigated the effect of tactile
signals on the internal representation of arm location at the behavioral level.

Many behavioral studies have provided clues as to the relationship
between tactile and proprioceptive signals. Tactile cues have been shown to
improve accuracy of pointing movements and estimations of hand location
(Helms Tillery et al., 1994; Jeka & Lackner, 1995; Lackner & Dizio, 1994;
Rabin & Gordon, 2004; Rao & Gordon, 2001; Rincon-Gonzalez, Buneo, &
Helms Tillery, 2011a; Ro et al., 2000), suggesting that tactile signals can
enhance proprioception. Conversely, proprioception has been shown to affect
aspects of tactile processing in that posture affects the perception of tactile
events (Aglioti, Smania, & Peru, 1999; Roberts & Humphreys, 2010; J. P.
Warren et al., 2011; S. Yamamoto & Kitazawa, 2001). For example, we have
shown that a tactile illusion elicited by electrotactile stimulation to the
fingertips could be eliminated by having subjects assume certain hand
postures (J. P. Warren et al., 2011). It remains unclear how the relationship
between touch and proprioception contributes to internal representations like
this, which in turn support and enhance physical interactions with the
environment.

One clue as to the structure of this representation comes from the
pattern of estimation errors when subjects estimate the location of their
unseen hands (Rincon-Gonzalez, Buneo, & Helms Tillery, 2011a; Rincon-
Gonzalez, Warren, Meller, & Helms Tillery, 2011b). Strikingly, the patterns of errors on a horizontal surface were constant and systematic across hands, time, and touch conditions. These results suggest long-term stability in the structure of this pattern of errors, which we refer to as the proprioceptive map of the arm. Several other sensorimotor studies that have also reported that errors in estimating hand location and end-point movements were constant and systematic (L. E. Brown, 2003; Desmurget et al., 2000; Helms Tillery et al., 1994; Rincon-Gonzalez, Buneo, & Helms Tillery, 2011a; van Beers et al., 1998; Wann & Ibrahim, 1992). In fact, research on visuomotor adaptation and motor learning has provided some insight into the stability and plasticity of this system: proprioception has been shown to adapt after visuomotor adaptations and motor learning (Cressman & Henriques, 2011; Mattar, Nasir, Darainy, & Ostryostry, 2011). Thus proprioception is stable to small everyday perturbations but flexible to long-term adaptations.

Here, we further examined the role of tactile signals on the proprioceptive map, by incorporating electrotactile feedback as one of the experimental conditions. To examine this issue, we reconstructed and analyzed the pattern of errors that resulted when subjects estimated the location of their unseen hand on a 2D horizontal workspace. Subjects made these estimates in three tactile conditions: 1) touching the surface of the workspace (Touch condition), 2) receiving electrotactile stimulation without touching the surface (Electrical condition), or 3) received no stimulation at all (No Touch condition). We have previously reported that tactile signals (touching the surface of the workspace) did not affect the structure of the
pattern of estimation errors (Rincon-Gonzalez, Buneo, & Helms Tillery, 2011a). In these experiments we asked whether the completely artificial sensation elicited with electrotactile stimulation could induce the effects we observed from the interaction between the proprioceptive and tactile sensing modalities, or whether the natural sensation arising from the contact of the fingertip with the surface was central to this interaction.

**METHODS**

In our psychophysical experiments, we reconstructed and analyzed the pattern of errors that resulted when subjects estimated their hand location across a 2D horizontal workspace. The setup and analyses have been previously described (Rincon-Gonzalez, Buneo, & Helms Tillery, 2011a) and are briefly summarized here.

In accordance with a protocol approved and monitored by the Arizona State University Institutional Review Board, seven right-handed subjects participated in an experiment with 3 tactile conditions in which their right hand was passively moved by the experimenter to 1 of 100 targets on a horizontal grid while their eyes were closed (Figure 3.1A). At each target location, one of three tactile conditions was applied before passively returning the subject’s hand to the resting position. Then, subjects were asked to open their eyes and verbally report the location where their hand had just been at by using the row letters, column numbers, and target colors (see Figure 3.1A). In the No Touch (NT) condition, the extended index finger was held by the experimenter 2 cm above the target for 5 seconds. In the Touch (T) condition, the subject’s index finger lightly touched the surface of the grid at the target
location for 5 seconds. In the Electrical (E) condition, electrical stimulation was applied to the fingertip while the finger was held above the target as in the NT condition (see Figure 3.1B). For this experimental condition, subjects were outfitted with a 3.2 mm diameter electrode centered on the volar aspect of the index finger on the distal phalanx and a reference electrode centered on the volar aspect of the same finger on the proximal phalanx. The waveform parameters were chosen (75 Hz, 0.5 ms duration) to maximize detectability. Prior to beginning the electrical condition, subject’s thresholds were determined to be the minimum current level at which the stimulus felt ‘electrical in nature’. Subjects were instructed to report if they stopped feeling the electrical stimulation during the experiment at which point the current amplitude was adjusted accordingly. This electrical condition was included to control for the fact that the proprioceptive information associated with NT and T were not completely equivalent. That is, the E condition provided tactile feedback while providing the same proprioceptive information as in NT. In each condition, no feedback was provided as to the actual location of the target. Each subject performed three experiments with the same set of 100 targets.
Figure 3.1. Experimental setup. (A) Horizontal surface grid used for the three experimental conditions: No Touch, Touch, and Electrical. Each square in the grid was labeled with a row letter (A-K), a column number (1-14), and four colored circles (red, green, yellow, and blue). A total of 616 targets were equally spaced from each other by 1.25 cm. (B) Diagram of stimulator connections and electrode setup for the electrical stimulation condition. A single round (3.2 mm diameter) electrode was centered on the volar aspect of the index finger on the distal phalanx and a reference electrode centered on the volar aspect of the same finger on the proximal phalanx.

To analyze the structure of the pattern of errors, we measured the direction and magnitude between the actual and estimated target locations, and then reconstructed the resulting pattern of errors as vector fields (see Figure 3.2). We measured the effect of the tactile conditions on the estimation errors by comparing two vector fields at a time. To this end, we first quantified the similarity of the resulting vector fields between two tactile
conditions using a vector correlation (VC) method (Buneo, 2011; Rincon-Gonzalez, Buneo, & Helms Tillery, 2011a). This method performs a pairwise correlation of two vector fields (e.g. NT vs. T or Figure 3.2A vs. Figure 3.2B) in which each pair of vectors at one target location is correlated. This VC method also accounts for any scaling, rotational, or reflectional relationship between the two vector fields. As a control, we randomized the spatial location of each of the vectors on one vector field before performing the correlation analysis between the two vector fields. In other words, we shuffled the vectors in Figure 3.2A before performing the correlation between this vector field and that in Figure 3.2B. In this analysis, a negative correlation coefficient indicates that the relationship between the two vector fields being compared is better explained by a reflection of one of the vector fields, while a positive correlation indicates that the relationship between the two vector fields is better explained by a rotation of one of the vector fields. To further examine the similarities between fields, we also analyzed the direction of the errors using a Kolmogorov-Smirnov (KS) test, which measures whether two cumulative distributions are different from each other. In this analysis, we superimposed the pattern of errors from two tactile conditions for one subject, in the same way as explained above, and measured the resulting absolute angle between each pair of superimposed vector errors. As a control, we used the same data-shuffling technique explained above. Then, we compared the non-randomized to the randomized (control) cumulative distribution of angles, in which a statistical difference indicated that the two non-randomized patterns of errors were more similar than would be expected by
chance. Finally, we used repeated-measures ANOVA with three levels (NT x T x E, df: 2099) where we pooled the 100 estimation errors for each of the 7 subjects (n = 700 trials per tactile condition), to analyze the effect of tactile condition on the magnitude of the estimation errors. We performed pairwise comparisons with the Bonferroni correction as a post hoc test.

RESULTS

We report that tactile cues did not significantly affect the structure of the proprioceptive map but touching the grid reduced the magnitude of the estimation errors. Figure 3.2 shows the resulting pattern of errors for one representative subject on the three experimental conditions. Panel A corresponds to the No Touch condition, panel B to the Touch condition, panel C to the Electrical condition, and panel D shows the three superimposed vector fields. This exemplary figure shows that the resulting pattern of errors from the three tactile conditions have a similar spatial structure. The figure also shows that the magnitude of the errors under the T condition is slightly smaller than that of the other two conditions. The statistical analyses support this observation. Table 3.1 shows the results from the Kolmogorov-Smirnov (KS) test and Vector Correlation (VC) analysis for the comparisons between tactile conditions for each subject. The values under the KS column represent the \( p \) values and the values under the VC columns represent the correlation coefficient for the non-randomized and randomized (control) comparisons. Under the VC analysis, all vector fields were highly correlated with one another as compared to the control condition, suggesting that touch and electrical stimulation had no effect on the overall structure of the pattern
of errors. The KS test also supported this conclusion. All comparisons but one were significantly more similar than would be expected by chance ($\alpha = .05$). Finally, the repeated-measures ANOVA test determined that the mean estimation error differed statistically significantly across tactile conditions ($F(2,1398) = 12.61, p < .0001$). The post hoc tests using the Bonferroni correction revealed that solely touching the grid resulted in significantly smaller estimation errors than in either E or NT conditions, while the E condition was not significantly different from the NT condition (NT vs. T: $5.76+/- .14$ vs. $5.06+/- .12$, $p = .0001$; NT vs. E: $5.76+/- .14$ vs. $5.80+/- .13$, $p = 1$; T vs. E: $5.06+/- .12$ vs. $5.80+/- .13$, $p = .00002$). Despite this change in accuracy, the overall structure of the map was independent of these tactile conditions.

**Figure 3.2.** Similarity of pattern of errors across tactile conditions.

Distribution of errors from one exemplary subject for the three experimental conditions. (A) Vector field of estimation errors for the No Touch condition,
(B) for the Touch condition, and (C) for the Electrical condition. (D) The three vector fields from A, B, and C superimposed.

Table 3.1

Test of Similarity Between Tactile Conditions (No Touch (NT), Touch (T), Electrical (E)). Resulting p-values from the Kolmogorov-Smirnov (KS) test and Resulting Correlation Coefficients (ρ) from the Vector Correlation Analysis for the Non-Randomized (“VC”) and Control (“VC_c”) Comparisons.

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DISCUSSION

The results presented here capture what we believe are key elements in this process of interpreting tactile and postural sensations to create a representation of the physical world. Spatial problems come with a frame of reference. In the proprioceptive task, we observed that when the natural tactile apparatus is engaged, the accuracy of spatial estimates is improved even though the overall structure of the estimates is not changed. This suggests that proprioception provides a stable frame of reference for somatic sensation. While proprioception is a three-dimensional spatial process existing in an intrinsic reference frame, tactile perception has only the two-dimensional somatotopic map provided by the skin to serve as a coordinate system. These intrinsic reference frames can be transformed into external reference frames when the tactile problem is essentially spatial. Thus, our view is that the interaction between deep and cutaneous senses takes place in a reference frame that is determined by the proprioceptive system.

Tactile input impacts, but does not disrupt, proprioceptive representations. In previous studies, we reported that touch did not affect the pattern of errors for either hand but it did decrease the magnitude of the errors when using the right hand only (Rincon-Gonzalez, Buneo, & Helms Tillery, 2011a; Rincon-Gonzalez, Warren, Meller, & Helms Tillery, 2011b). We concluded that the spatial structure of proprioception was subject-specific, stable across hands, tactile conditions, and time. Here we report that electrotactile stimulation did not affect the direction or magnitude of the estimation errors. Therefore, all these results taken together suggest that
subjects estimate the location of their hands using a stable proprioceptive representation of their arms, one which is not spatially affected by touch. This conclusion is in agreement with the idea that one of the features of the internal body representation is to be conservative and stable (Carruthers, 2008; Ivanenko et al., 2011).

Although the direction of the errors did not change in any of the three conditions, the Touch condition resulted in a decrease of the error magnitude. There were two main differences between Touch and Electrical conditions that could account for this observed effect. First, in the NT and E conditions the experimenter held the subject’s hand 1-2 cm above the target while in the T condition the experimenter lowered the hand until it made contact with the workspace. It is possible that the muscular activity between these two manipulations was different. However, we do not believe it was a major difference as the experimenter held on to the subject’s hand throughout each trial for the three conditions. It is also possible that the proprioceptive information was different between these two positions. Although we did not control the arm posture at each target, it is unlikely that the 1+/1 cm difference made a significant difference in arm posture. Second, the tactile feedback provided by touching the table in the T condition and the one provided by the electrotactile stimulation were perceived differently. Touching the finger to the workspace activated mechanoreceptors on the skin while electrotactile stimulation to the surface of the skin probably activated the mechanoreceptors’ afferents. Earlier results had suggested that the direction of shear on the fingertip was an important component of the effect.
of tactile input in reducing error in estimating hand location (Lackner & Dizio, 2000). This seemed implausible because in many of the tasks, the shear was either nominal, or always directed along the long axis of the finger, thus providing no clear spatial information that varied with hand location. Here we reasoned that if shear on the fingertip were the key element, removing the shear while providing tactile stimulation should result in a return to the magnitude of error observed with no tactile input since electrotactile stimulation would provide tactile stimulation with no deformation of the skin.

What Does The Psychophysics Suggest About The Combination of Kinesthetic And Tactile Signals? It is a standing observation that contact of the fingertip with a surface improves performance on a variety of spatial and dynamic tasks, provided that surface is assumed to be stable (Jeka & Lackner, 1995; Lackner & Dizio, 1994; Rabin & Gordon, 2004). This is perhaps not surprising, as the external environment has more spatial stability than our bodies. It is puzzling, though, that touching a finger to a surface (even if contact is achieved through passive movement of the hand by an experimenter) should reduce the error in knowing where that finger is in space (Helms Tillery et al., 1994; Rincon-Gonzalez, Buneo, & Helms Tillery, 2011a; Rincon-Gonzalez, Warren, Meller, & Helms Tillery, 2011b). The location in space of the index finger, for example, depends on the state of a serial chain of joints. Touching the finger to a surface does not have any clear ramifications for joint angle sensors when posture remains
constant. Instead, it appears that touching the skin invokes additional somatosensory processing.

One possibility is that touching the surface changes the estimation task itself. When the hand is held over some location, estimating the location of the fingertip is a truly proprioceptive problem: information about the states of the joints must be derived from a variety of sensors, and that information integrated to estimate the location of the fingertip relative to the rest of the body. Once the finger is touched to a surface, we are no longer estimating the location of the fingertip but are rather estimating an external location in space and the properties of the surface being touched by the finger. While the sources of information are largely the same, the processing appears to be different: the nervous system is now explicitly processing the signals to determine the spatial location of the hand, all the while assuming a stable set of cues in the environment. That is, with contact between the fingertip and the environment, the estimation task transitions from one of posture in an intrinsic reference frame to one of spatial location of the hand in an extrinsic reference frame.

Thus, we show here important insights into the interaction between proprioception and touch. The observation that proprioceptive estimates of hand position are spatially robust to tactile conditions indicates that somatospatial problems utilize a stable frame of reference, which is provided by the proprioceptive system. We propose that the tactile sensations, which underlie haptics, are processed in a reference frame that is provided by the proprioceptive system. While the spatial structure of the proprioceptive map
is essentially stable, the representations underlying object perception depend on posture, and are thus likely dynamic. Elucidating the interactions between tactile and proprioceptive representations will be useful for understanding the consequences of dysfunction in each of the two systems, and will be necessary for providing both stable and adaptive sensory feedback in neuroprosthetic applications.
Chapter 4

VISUOMOTOR ADAPTATION STUDY

INTRODUCTION

Perception of our body is essential for interacting with our surroundings as it allows us to perceive the location of our body parts in space and to control our spatial actions. An example of this is our ability to perceive and act on the external location of a touched body surface: when using one hand to swat a fly that landed on the other arm, the brain must integrate tactile information elicited from the skin contact with the fly, proprioceptive information about the current posture of both arms, and information about the length and width of the touched arm. However, neither tactile nor proprioceptive receptors provide such information about body size. Perceiving and acting on an external location of a touched body surface requires a combination of afferent information and stored representations of the body. Since relatively little is known about the structure of these stored representations, here we aimed to provide insight into this structure by probing its calibration and stability.

Internal representations of the body are most likely constructed through a multisensory process involving visual, tactile, and proprioceptive information. Insight into this process comes from studies using the crossmodal congruency task that have investigated the interaction between proprioception and the representation of visuotactile space in relation to the perception of limb position and its surrounding space (Kennett et al., 2002; Maravita et al., 2003; Spence et al., 2004). In this task, subjects hold two
foam cubes, one in either hand, between their index finger and thumb. Subjects had to make a series of speeded elevation discrimination responses about vibrotactile stimulation delivered to their index or thumb across different postures of their unseen arms while ignoring visual distractors presented at either the left or right hemifields. What these studies have shown is that proprioceptive, tactile, and visual information came together to provide information as to whether the light source was in the same spatial location as the stimulated hand. This result suggests that internal representations of body parts and of the surrounding space are based on the integration of visual, tactile and proprioceptive information.

There is currently some debate in the literature regarding whether these sensory modalities come together to form one internal representation of the body or whether there are multiple internal representations that continuously interact with each other. Based on our previous studies, it is our contention that proprioception provides the underlying stable framework for the internal representation of arm location, which interacts with the more dynamic tactile and visual representations. Therefore, the main goal of this present experiment was to probe the stability of the structure of the internal representation of arm location.

We have previously shown that the internal representation of arm location can be studied through the analysis of the spatial structure of estimation errors in our proprioceptive estimation task. In a set of experiments, we analyzed and reconstructed the pattern of estimation errors that resulted when subjects estimated the location of their unseen hand
across a 2-D workspace (Rincon-Gonzalez, Buneo, & Helms Tillery, 2011a). Our analyses of the structure have confirmed observations (L. E. Brown, 2003; L. E. Brown et al., 2003; Desmurget et al., 2000; Haggard et al., 2000; Helms Tillery et al., 1994; Smeets et al., 2006; van Beers et al., 1996; 1998; Vindras et al., 1998; Wann & Ibrahim, 1992) that these errors are remarkably stable, symmetric across the hands, non-uniform across the workspace, and subject specific. In agreement with other studies (Fuentes & Bastian, 2010; Helms Tillery et al., 1994; van Beers et al., 1998; 2002; Wilson et al., 2010), our results also showed that on average subjects’ estimations are non-uniform across the workspace: errors are smallest when targets are located closer to the body. However, at the single subject level we observed that the workspace locations for the minimum and maximum estimation errors were distributed differently across subjects.

Taken together, our previous results suggest that the observed spatial structure of the pattern of errors is constructed using one global and stable solution that is being continuously calibrated non-uniformly across the workspace. The idiosyncrasy in the pattern of errors shapes the entire spatial structure and not just the larger errors at the periphery, which one might expect in the case of a set of local solutions. The idiosyncrasy of the spatial structure of the pattern of errors suggests that each individual’s internal mapping is uniquely constructed through a learning mechanism and thus it is the result of individual experience. The observed common themes on the structure of the map suggest that the spatial structure of estimation errors is a consequence of a system that is continually calibrating the proprioceptive
representation of hand location. The area where we get the greatest amount of exposure is where the calibration will be best. Therefore we seek to determine if we can perturb the stability of the structure of the proprioceptive map of hand location and whether the effect of the perturbation varies across the workspace. To this end, we propose to use a local visuomotor adaptation to perturb this structure. We hypothesize that if we can perturb the proprioceptive map at that location, we will observe a generalization of the adaption to the rest of the map, which is indicative of a global solution. However, we hypothesize that this pattern of adaptation will be non-uniform because there are areas on the workspace that will be more robust to the perturbation than other areas.

In a visuomotor adaptation task subjects learn to reach to a target with misaligned visual feedback of the hand and thus adapt to the imposed misalignment between vision and proprioception. It has been shown that visuomotor adaptations not only can recalibrate the sensorimotor transformations underlying reaching movements, but also recalibrate proprioception (Cressman & Henriques, 2009; 2010). Similarly, other motor learning paradigms have shown that motor learning results in proprioceptive change (L. E. Brown, Wilson, Goodale, & Gribble, 2007; Cressman & Henriques, 2009; 2010; Haith, Jackson, Miall, & Vijayakumar, 2008; Malfait, Henriques, & Gribble, 2007; Ostry et al., 2010; Simani, McGuire, & Sabes, 2007; van Beers et al., 2002; Wong et al., 2011). In our proposed experiments, a visuomotor adaptation should lead to a change to the internal representation of the body’s position in space.
Visuomotor adaptation has also been used to study the degree of spatial generalization across the workspace, which has been suggested to provide insight into the structure of internal representations of mappings (Donchin, Francis, & Shadmehr, 2003; Poggio & Bizzi, 2004; Shadmehr, 2004). Spatial generalization refers to the extent to which movements to unpracticed regions in the workspace are affected by previous adaptation to localized regions. Visuomotor generalization studies that examined the pointing behavior at different locations in the workspace after local visuomotor adaptation, have reported limited adaptation to the untrained regions of the workspace (Cressman & Henriques, 2010; Ghahramani, Wolpert, & Jordan, 1996; Ghilardi, Gordon, & Ghez, 1995; Krakauer, Pine, Ghilardi, & Ghez, 2000; Pearson, Krakauer, & Mazzoni, 2010). Studies on generalization in dynamics learning have also shown that motor learning generalizes to movements in novel locations in the workspace (Mattar & Ostry, 2007; Shadmehr & Mussa-Ivaldi, 1994). In our proposed experiments, local perturbations to the structure of the map should propagate throughout the map just like the idiosyncrasy of the errors. Generalization patterns after visuomotor adaptation should probe the non-uniform and idiosyncratic quality of the structure of the proprioceptive map.

In the present study, we have examined the effect of a visuomotor adaptation on the pattern of errors that resulted when subjects estimated the location of their unseen arm in a 2-D workspace composed of 16 target locations. The direction and magnitude of the estimation errors were assessed before and after exposure to a localized visuomotor perturbation.
located in the middle of the workspace. The local perturbation was achieved by having subjects reach to a location on the 2-D surface of a horizontal table, which was virtually displayed on a computer monitor located in front of their working space.

**METHODS**

**Subjects.** Seven [mean age: 23.3 yr] students from Arizona State University participated in the experiment; one male and four females received the perturbation, while one male and one female served as controls for the effect of training during the adaptation tasks. Only subjects who verbally stated being right-handed and free of any history of visual, sensorimotor or neurological conditions were recruited. All subjects signed written informed consent documents before each experiment. The Institutional Review Board at Arizona State University approved this study.

**Figure 4.1.** Experimental tasks. Schematic showing the order in which the different tasks were completed. Part 0 and Part 1 provided baseline measures
of performance. The second part of the second session consisted on the perturbation and post perturbation measures of performance.

**General Experimental Setup and Procedures.** For all subjects, the experiment was completed in two separate testing sessions, which were separated by 4+/−1 days. Each session and its parts are described in the following text and illustrated in Figure 4.1. The first session consisted solely on capturing the baseline proprioceptive map while the second session consisted on a capturing a proprioceptive map (PM) before and after the Visuomotor Adaptation (VA). The second session consisted on two parts with four tasks each. The first part served as a baseline measure for both the estimation errors in the proprioceptive map and the reaching errors in the 2-D Virtual Reality (VR) setup. The second part consisted of the VA and PM following VA. Both sessions were carried out on the same table in the same experimental room, which was equipped with a motion capture system (3 Optotrack 3020 camera bars, Northern Digital Inc) to record arm movements. Upon arriving to the laboratory, subjects were informed that their perceptual and motor coordination was going to be tested before and after reaching movements in a VR environment. Then, they received a brief description of the PM and VA tests, without actually telling them about the perturbation.

**Proprioceptive Setup and Procedures.** The proprioceptive setup is illustrated in Figure 4.2, and is similar to that used in Rincon-Gonzalez et al. (2011) (Rincon-Gonzalez, Buneo, & Helms Tillery, 2011a). This set up consisted on a board with a color-printed grid, marked with A through K rows and 1 through 18 columns. Each square on the grid was 5 by 5 cm and had
four colored targets (0.7 cm in diameter) located 1.25 cm from the edges of each square and 2.5 cm from each other along the horizontal (x) and depth (y) directions, resulting in 766 targets. The grid dimensions were 90 cm in the x direction and 50 cm in the y direction, but because of curvature, the depth of the grid was 55 cm at the midline (x = 45 cm).

Figure 4.2. Estimation task setup. This set up consisted on a board with a color-printed grid, marked with A through K rows and 1 through 18 columns. Each square had four colored targets. Also shown here are the 16 target locations used. The circled target corresponds to where the local perturbation was applied.

Subjects sat 10 cm in front of the grid, making sure their midline was aligned to the grid’s midline, which corresponded to the line between 9 and 10 (x = 45 cm). Subjects were instructed to sit straight and to keep their backs against the chair’s backrest. Their left hand rested on their laps while their right hand assumed a pointing position throughout the experiment. In
between trials, subjects rested their extended right index finger on the lower right corner of the grid, which was considered the resting position. Before the session started, subjects were instructed to keep their eyes closed at all times while their arm was being moved and to only open their eyes when their arm was back at the resting position. During an experiment, the experimenter stood to the right of the subject and only grabbed the subjects’ wrist before each trial. On each trial, the experimenter grasped the subject’s wrist and passively moved the pointing finger to a target location on the grid, where the experimenter lightly pressed the subject’s fingerpad to the target for about 5 seconds before returning the hand to the resting position. At this point, subjects opened their eyes and verbally reported the target location of where they thought their hand had been previously at by using the column letters, row numbers, and target colors. Subjects never received feedback as to the correct location of the target. There were three PM sessions, with 80 trials each. Each session consisted of 5 repetitions to the same 16 targets, which were evenly spaced throughout the reachable workspace (Figure 4.2). The targets were semi-randomly presented to all subjects such that all 16 targets were randomly presented before any of them were repeated. The same target set was used in the same order for all subjects. All of the trials were performed by the same experimenter, who strove to keep the passive displacement constant and without significant change between trials and sessions. No specific path or trajectory was used to move the hand to and from the target.
Visuomotor Adaptation Setup and Procedures. Subjects came back three to five days later to perform the testing session. The first part of this session (Part 1) served as the baseline and was used to assess reaching errors in the VR game and to capture the second baseline of the proprioceptive map (PM). The second part (Part 2) introduced the visuomotor adaptation and was used to assess reaching errors in the VR and estimation errors in the PM after the VA. The experimental set up (see Figure 4.3) consisted on a detachable black board (x: 89.6 cm; y: 55.11 cm) that sat on the same table used during the first session. There were four motion tracking markers on every corner of the black board, which were used to calculate the finger position with respect to the board and to display this finger position on the computer screen. The initial position was marked on the board with thick double-sided tape and was located on the board at 1 cm from the lower and right edges of the board. This location was meant to overlap in space with the resting position used for the proprioceptive map (estimation task). On another table, located behind the experimental table, sat a monitor raised to be at eye level.

Figure 4.3. Visuomotor perturbation setup. (A) This panel shows the apparatus used during the visuomotor tasks. Subjects sat in front of the table
and made reaching movements along the surface of the table. (B) This panel shows the reaching movements made during the pre-perturbation, exposure to misaligned feedback, and post-perturbation tasks. The subject’s view of their arm and movements was blocked with a board. The black arrows represent the terminal feedback of the finger movements. The grey arrow on the small screen represents the misaligned terminal feedback of the finger movements. The red arrow represents the actual movement of the hand at the end of the misaligned trial.

For all the experimental parts in the second session, subjects sat in front of the table and computer monitor. All experiments were performed on the dark and thus subjects could only see the colored circles on the screen. A motion-tracking marker was attached to the right index fingernail to record the finger trajectory to and from the initial position; the marker was taken off during PM sessions. This marker was displayed on the monitor screen as a white circle of 5 mm radius on an otherwise black screen. Before the start of the session, the resting position was calibrated by having subjects move the white circle on the screen (cursor representing their index finger) to the initial position, displayed as an orange circle of 5 mm radius, and to keep the white circle over the orange circle for 5 seconds. The initial position (orange circle) was displayed at the bottom right corner of the screen and matched the physical location of the initial position on the black board.

The VR game was designed to display a black screen (1280x998 pixels), which represented a scaled down version of the black board and proprioceptive grid (90 cm by 50 cm). Before each part of the experiment, the
experimenter entered into the game GUI the number of reaches and the location of the target on the screen. The location of any target on the screen, matched the physical location of that target on the proprioceptive grid based on a scaling factor. The chosen target to be perturbed was G11b, which was located at $x = 53.75$ cm and $y = 31.16$ cm on the board measured from the left bottom corner (see Figure 4.2). On the screen, this target was displayed at $x = 728$ pixels and $y = 567$ pixels measured from the left bottom corner of the screen.

For all tasks, subjects were told to keep their finger in contact with the black board at all times and not to lift it off the board when reaching towards a target. In other words, they were asked to trace the surface of the board from the initial position to the target. Lifting off their finger from the board would have affected the visual feedback of their finger position as the VR game could only work in the 2-d plane of the table and any movements in the $z$-component could significantly alter this feedback. Only tactile feedback was provided as to the location of the initial position but not as to the location of the target. View of their hand was occluded with a vertical board attached to the edge of the table, in which its edge was aligned with the subject’s right shoulder and thus allowed subjects to freely move their right arms around the vertical board without visual feedback of their arm movements. Vision of the initial position was not occluded but was difficult to see in the dark. Subjects were asked to keep their eyes on the screen and not to look at the black board or their hands.
At the beginning of a trial, subjects saw the orange circle that represented the initial position. A trial did not start until the cursor representing the finger (the white circle) / index finger was positioned over the orange circle/physical initial position and kept stationary for 1 second. After this time had elapsed, the orange circle disappeared from under the white circle and a red circle representing the target appeared on the screen. This signaled subjects to reach towards the red circle with fast but accurate movements and to position the white circle over the red circle at the end of the movement. Once at the target, they had to hold the finger cursor still for 1 second before the target disappeared and the initial position reappeared to signal the beginning of the next trial.

**Part 1: Task 1. Reach Familiarization task: Continuous visual feedback of veridical finger position.** The purpose of this task was to allow subjects to get familiar with the VR setup and with making 2-D reaching movements on the black board. These data were not included in our analysis. In this task, subjects made 5 reaching movements towards the target, as described above. In this case, both the target (red circle) and cursor representing the finger (white circle) were displayed throughout the movement and thus subjects had continuous feedback of their finger and target location.

**Part 1: Task 2. Reach Training task: Terminal feedback of veridical finger position.** This task served as a control for the reaching movements experienced during perturbation. To this end, boxes 2 and 3 in Part 1 (Figure 4.1) were designed to elicit the same in and out reaching movements as in
boxes 1 and 2 in Part 2 (except for the perturbed cursor feedback). In other words, if there are no changes in the errors in P2 compared to P1 then we can be confident that any changes found on P3 did not come from the reaching movement themselves experienced in boxes 1 and 2 in Part 2 but from the actual perturbation. This task started with the appearance of the orange circle and white circle on the screen, which represented the location of the initial location and fingertip. After 1 second, both the orange and white circles disappeared and the target appeared as a red circle, which indicated the start of a trial. The subject was then to reach to the target, which was shown on the screen for the duration of the reach. The cursor representing the fingertip (white circle) reappeared once the finger was 3 cm from the target (red circle). The computer program was designed to display the location of the finger as soon as the white circle entered into a 30 cm radius cloud surrounding the target. Once the subject reached the target and held the finger at the target for 1 second, the white and red circles disappeared and the orange circle reappeared. This indicated the end of a trial and instructed the subject to go back to the initial position. Subjects completed 50 trials to a single target with terminal feedback of their finger location.

**Part 1: Task 3. Reach Aftereffects 1: No visual feedback of finger position.** The purpose of this task was to measure the reaching errors in the absence of visual feedback of finger position. Any errors observed during this task could be attributed to a subject’s ability to estimate the location of their unseen finger and thus could indicate any potential intrinsic biases. Therefore, these errors served as the baseline for subjects’ reaching
performance pre VA. Each trial was carried out as described above except that the white circle representing the finger was never displayed. Subjects were instructed to end the reach by holding the finger position at whichever location they thought corresponded to the target location. They were able to find the initial location on the blackboard based on the tactile feedback provided by the tape. Subjects completed 15 trials to a single target with no visual feedback of their finger position.

**Part 1: Task 4. Proprioceptive mapping 2 (P2): baseline 2.** This task was performed after a short break. During the break, the occluding board was removed, and the black board was lifted off the table and switched with the proprioceptive grid. The marker on the fingertip was removed during this task. In addition, lights were turned ON so the subjects could see the grid. The proprioceptive mapping was performed as described above.

**Part 1: Task 5. Reach Aftereffects 2: no visual feedback of the finger position.** After switching back the black board and attaching the obstructing board and finger marker, the subjects once again performed a series of VR reaches with no visual feedback of the position of their finger. The purpose of this task was to measure reach errors and to control for any effects of the proprioceptive map or any intrinsic variability between tasks. Each trial was carried out as described in Task 3.

**Part 2: Task 6. Reach Training: visual feedback of PERTURBED cursor position.** This task consisted on the visuomotor adaptation, which followed the same steps as in the reach training task (task 2) described previously. However, instead of providing veridical terminal feedback of the
finger location, terminal feedback of the finger was perturbed on the negative x direction. The cursor perturbation was introduced gradually over the course of the task by increments of -1 mm (to the left of the target from the subject’s point of view) until the full -5 cm were reached by trial 50. The remaining 50 trials kept the perturbed cursor at -5 cm from the actual location of the finger. Therefore, the total perturbation at the end of the training was 5 cm to the left of the actual finger location on the x-direction only. Subjects completed 100 trials to a single target with 30 mm terminal feedback.

*Part 2: Task 7. Reach Aftereffects 3: No visual feedback of the finger position.* The purpose of this task was to measure the reaching errors after the perturbation as a measure of the adaptation aftereffects. This task was carried out as explained in task 3.

*Part 2: Task 8. Proprioceptive mapping 3 (P3): post adaptation measure.* This task represents our experimental measure, which measured the effect of VA. This task was carried out as explain in task 2.

*Part 2: Task 9. Reach Aftereffects 4: No visual feedback of the finger position.* The purpose of this task was to measure the reaching errors after the visuomotor perturbation and the post VA-proprioceptive map (P3) as a measure of the persistence of the adaptation effects. This task was carried out as explained in task 3.

**Analysis.**

**Visuomotor Adaptation.** During an experiment, six motion capture markers were used to record 3-D position and movement data: one marker on the index finger, 4 markers on the edges of the black board, and one reference
marker. The marker on the finger was used to record the subjects’ reaching movements on each trial in the VR tasks. Since the VR game displayed a 2-d representation of the finger and board space, we only used the x and y components of the finger movements captured with the motion tracking cameras. To this end, subjects were asked to keep their reaching movements on the table without lifting the finger off the table.

We analyzed reaching errors made in each VR task to determine whether 1) subjects accurately reached the target with terminal feedback of the finger cursors, 2) subjects had any intrinsic bias when reaching to the target with no visual feedback of the finger cursor, 3) subjects reaches were affected by the reach training trials or the proprioceptive mapping, 4) subjects adapted their reaches after training with the perturbed cursor, and 5) reach adaptation was maintained after the last proprioceptive map session. To this end, we calculated the endpoint in the x and y direction of the finger reaches when subjects paused to indicate the end of the trial. We analyzed the mean reach errors for 8 analysis groups, as shown in figure 4.4 and listed below:

1) Reach Training: To determine whether subjects could accurately reach the target with terminal feedback (Figure 4.1: box 2, part 1) we subtracted the mean endpoint screen coordinates (in pixels) of the finger cursor from the screen coordinates of the target location.

2) Pre PM2 (N1): To determine the accuracy of the reaches in the absence of visual feedback during this task (Figure 4.1: box 3, part 1) we
subtracted the mean endpoint screen coordinates (in pixels) of the finger cursor from the screen coordinates of the target location.

3) Pre Pert (N2): To determine how much the reaches changed after the second proprioceptive mapping (Figure 4.1: box 5, part 1), we subtracted the mean endpoint screen coordinates (in pixels) of the finger cursor from the screen coordinates of the target location.

4) N2-N1: To determine the magnitude of the change in reach errors between the first two Reach Aftereffect tasks, we found the difference in the mean endpoint screen coordinates of the finger cursor between Reach Aftereffects 1 (Figure 4.1: box 3, part 1) and Reach Aftereffects 2 (Figure 4.1: box 5, part 1).

5) Pert: To determine whether subjects could accurately reach the target with the perturbed cursor feedback (Figure 4.1: box 1, part 2), we subtracted the mean endpoint screen coordinates (in pixels) of the finger cursor from the screen coordinates of the target location.

6) Post Pert (N3): To determine the magnitude of the adaptation, we subtracted the mean endpoint reaches during Reach Aftereffects 3 (Figure 4.1: box 2, part 2) from the average mean endpoint between Reach Aftereffects 2 and Reach Aftereffects 1 (Figure 4.1: boxes 3 and 5, part 1).

7) N4-N3: To determine how much the adaptation was maintained after the last proprioceptive mapping with respect to the Reach Aftereffects 3 task, we subtracted the mean endpoint screen coordinates of the finger cursor in Reach Aftereffects 4 (Figure 4.1: box 4, part 2) from the mean endpoint errors in Reach Aftereffects 3 (Figure 4.1: box 2, part 2).
8) Post PM3 (N4): To determine how much the adaptation was maintained after the last proprioceptive mapping with respect to Reach Aftereffects 1 and 2, we subtracted the mean endpoint reaches during Reach Aftereffects 4 (Figure 4.1: box 4, part 2) to the average mean endpoint between Reach Aftereffects 2 and Reach Aftereffects 1 (Figure 4.1: boxes 3 and 5, part 1).

We converted the units from pixels to cm by using 33.4 cm/pixels as the conversion factor. Finally, we performed two one-way ANOVA tests to examine the question of whether reach endpoints differed along the x-direction and y-direction for the following groups as seen in Figure 4.4: 1) Reach Training; 2) Pre PM2 (N1); 3) Pre Pert (N2); 4) Pert; 5) Post Pert (N3); and 6) Post PM3 (N4). We also performed independent t-tests between the x- and y-directions for each of these groups separately.

**Proprioceptive Mapping.** A change in the proprioceptive map was measured as the difference in performance between the baseline maps (P1, P2) and the post VA map (P3). In other words, we compared box 1 in part 0, box 4 in part 1, and box 3 in part 2 as seen in Figure 4.1. Performance was evaluated by measuring the direction and magnitude of the errors between the actual and estimated target locations.

**Vector Correlation.** We first quantified the degree of similarity between the patterns of errors across the three PM sessions for each subject by using a vector field correlation method (Buneo, 2011; Rincon-Gonzalez, Buneo, & Helms Tillery, 2011a). This nonparametric method involves a pairwise vector correlation between each target location across two vector
fields that takes into account the irregularities and asymmetries in the fields in order to quantify the degree of rotational or reflectional dependence and the scaling relationship between them. A correlation coefficient of 1 indicates a perfect rotational relationship, while a coefficient of -1 indicates a perfect reflectional relationship. A small angle of rotation/reflection, θ, indicates that the two vector fields are minimally rotated/reflected with respect to each other. Finally, the scaling factor β is formed from the ratio of the variances of the two sets of vectors and indicates the scaling relationship between the two vector fields.

**Effect of Visuomotor Adaptation on the proprioceptive mapping.**

*Mean magnitude of the estimation errors.* To determine if the local perturbation had an effect on the proprioceptive map at the target location that spatially matched the location of the visuomotor perturbation or at any other target location, we analyzed the magnitude of the errors at each target location across the three proprioceptive mappings for each subject separately with a 3 time (proprioceptive maps before and after VA: P1, P2, P3) x target location (16 targets) repeated-measures analysis of variance (RM-ANOVA). As a pot-hoc test, we performed separate RM-ANOVAs for each target location across the three proprioceptive sessions, which resulted in 16 different comparisons. We corrected for the multiple comparisons using the method explained below. Since the perturbation was applied on the x-direction only, we also analyzed the effect of the VA for the x- and y-component of the error vector. To this end, we used a 3 time (proprioceptive
maps before and after VA: P1, P2, P3) x target location (16 targets) RM-
ANOVA for each component and subject separately. Finally, we also analyzed
the pooled data across subjects to determine if the common themes on the
structure were affected by the perturbation. To this end, we performed the
same RM-ANOVA as described above on the pooled data for the magnitude,
x-component, and y-component of the error separately.

**Mean direction of the estimation errors.** In addition to analyzing the
effect of PA on the magnitude of the errors, we also quantified this effect on
the direction of the errors. To this end, we performed circular statistics across
target locations and between vector fields on the data from each subject as
well as on the pooled data across subjects. For the single-subject analysis, we
compared the angle formed between the azimuth (0°) and the vector error
(see equation 1) at each target location between two PM sessions (P1 vs. P2,
P1 vs. P3, P2 vs. P3). Appropriate measures were taken in the case where the
x or y components of the error vector were zero or when they were negative.
Then we analyzed the resulting angles with the Watson-Williams
multisample test, which is the circular analogue of the one-factor ANOVA
test. Since there are not circular analogues of post hoc tests, we compared the
angles between two PMs for each target separately, which resulted in 48
multiple comparisons for each subject (3 statistical tests at each of the 16
target locations). As a result of the multiple comparisons, we used the
Benjamini-Hochberg procedure to control the false discovery rate (FDR).
First, we ranked the individual $p$-values from each of the 48 comparisons in
ascending order. Then, we compared each individual $p$-value to the FDR
equation (equation 2), in which $P$ corresponds to each individual $p$-value, $i$ corresponds to the ranking of each $p$-value, $m$ corresponds to the number of multiple comparisons, and $q^*$ corresponds to the $\alpha$ level at which we are controlling the probability of type I errors. Here, we set $\alpha$ to be .05.

$$\alpha = \tan^{-1}(x/y)$$

(1)

$$P(i) \leq \frac{i}{m}q^*$$

(2)

In order to quantify the effect of the VA on the mean direction of errors across the whole workspace, we pooled all the errors for each map. However, we could not pool the errors without accounting for the non-uniformity and idiosyncrasy of the map first. To this end, we removed this non-uniformity and idiosyncrasy by looking at the change in angle from one map to the other at each target location instead of looking at the actual direction of the error. In other words, we found the angle between the mean estimation errors at each target location across two PMs. For example, we computed the angle formed between the mean error vector at target # 5 in P1 and the mean error vector at the same target location in P2. We then analyzed those 16 changes in direction across the three PM sessions with a Watson-Williams multisample test.

**Variable Error of the estimation errors.** Finally, we established the variability in performance and the effect of the adaptation on the variable error. To this end, we performed a 4th order regression analysis on the data from each of the subjects and on the pooled data across subjects. The regression equations were used to compute the variable error as follows:
\[ X_{\text{fit}} = x^4 + x^3 y + x^2 y^2 + xy^3 + y^4 + x^3 + x^2 y + xy^2 + y^3 + x^2 + xy + y^2 + x + y \] (3)

\[ Y_{\text{fit}} = x^4 + x^3 y + x^2 y^2 + xy^3 + y^4 + x^3 + x^2 y + xy^2 + y^3 + x^2 + xy + y^2 + x + y \] (4)

\[ E_{x^2} = \frac{1}{n} \sum_{i=1}^{n} (X_{\text{data},i} - X_{\text{fit},i})^2 \] (5)

\[ E_{y^2} = \frac{1}{n} \sum_{i=1}^{n} (Y_{\text{data},i} - Y_{\text{fit},i})^2 \] (6)

\[ E_{\text{tot}^2} = \frac{1}{n} \sum_{i=1}^{n} \left( (X_{\text{data},i} - X_{\text{fit},i})^2 + (Y_{\text{data},i} - Y_{\text{fit},i})^2 \right) \] (7)

We then analyzed the variance in \( x \) (\( E_{x^2} \)), \( y \) (\( E_{y^2} \)) and the total variance (\( E_{\text{tot}^2} \)) with a 3 time (proprioceptive maps before and after VA: P1, P2, P3) repeated-measures analysis of variance (RM-ANOVA). We also used an independent t-test between \( E_{x^2} \) and \( E_{y^2} \) for each proprioceptive map.

**RESULTS**

**Visuomotor Adaptation.** In order to determine if the Visuomotor Adaptation (VA) had an effect on the proprioceptive map (PM), we first had to determine the extent to which subjects adapted to the VA exposure. We also analyzed the mean reach errors at each VR task. Figure 4.4 shows the mean reach endpoint errors for each of the analysis groups as explained in the methods section, where positive values correspond to the right of the target (direction of the perturbation) and negative values correspond to the left of the target. We performed two one-way ANOVA tests to examine the question of whether reach endpoints differed along the x-direction and y-direction for the following groups: 1) Reach Training; 2) Pre PM2 (N1); 3) Pre Pert (N2); 4) Pert; 5) Post Pert (N3); and 6) Post PM3 (N4). For the x-axis group, the
Levene’s $F$ test revealed that the homogeneity of variance assumption was not met ($p = .003$), and thus we used the Welch’s $F$ test and the Games-Howell post-hoc test. There was a statistically difference between groups as determined by one-way ANOVA (Welch’s $F(5,9.364) = 57984.526, p < 1e^{-6}$). A Games-Howell post-hoc test revealed a significant difference between the mean reach endpoint errors during perturbation ($pert$) and every other group. There was also a significant difference between the mean reach endpoint errors measured after the perturbation at the Aftereffects 3 task ($Post Pert (N3)$) and groups 1, 2, 3, and 4. For the y-axis group, the Levene’s $F$ test revealed that the homogeneity of variance assumption was not met ($p < .0001$), and thus we used the Welch’s $F$ test and the Games-Howell post-hoc test. There was not a statistically difference across the y-axis groups as determined by one-way ANOVA (Welch’s $F(5,9.431) = 1.751, p = .215$).

Finally, we performed independent $t$-tests between x- and y-directions for each group separately. For the perturbation group, the x- and y-directions were significant different ($t(8) = 319.317, p < .0001$). For the post perturbation group, the x- and y-directions were significant different ($t(8) = 6.407, p < .0001$). The rest of the comparisons were not significantly different.
Figure 4.4. Visuomotor adaptation. Mean reach endpoint errors for each of the analysis groups as explained in the methods section, where positive values correspond to the right of the target (direction of the perturbation) and negative values correspond to the left of the target. Error bars reflect the standard error of the mean. * Significant difference between Pert and groups 1-3, 5, and 6 as well as between Post Pert (N3) and groups 1-4 as revealed by the RM-ANOVA on the x-axis only. ** Significance difference between X- and Y-axis for the Pert and for the Post Pert (N3) as revealed by independent t-tests.

Taken together, these results suggest that in average subjects adapted 50% to the visuomotor perturbation in the x-direction. Subjects were able to accurately reach the target during the Reach Training task, which provided terminal visual feedback of the cursor. Although some subjects showed some intrinsic bias in their reaches, as observed during the first two Aftereffects.
tests (Pre PM2 and Pre Pert), the resulting endpoint reaches were not significantly different from the accurate reaches observed during Reach Training. Similarly, subjects’ reaches were not affected by the proprioceptive mapping before perturbation. Finally, the adaptation decayed by 50% of the observed aftereffects after P3. This value was only significantly different from the full adaptation observed during exposure. Table 4.1 shows the amount by which each subject adapted to the perturbation as measured by comparing the endpoints post perturbation at N3 to the endpoints pre perturbation (average between N2 and N1). This table also shows the magnitude of the adaptation observed after the last proprioceptive mapping. All these results suggest that in average subjects adapted to 50% of the perturbation and 50% of this adaptation remained at the end of the experimental session.

Table 4.1

<table>
<thead>
<tr>
<th>Subjects</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptation</td>
<td>2.35</td>
<td>2.37</td>
<td>2.39</td>
<td>1.87</td>
<td>3.42</td>
</tr>
<tr>
<td>Sustained</td>
<td>1.45</td>
<td>0.08</td>
<td>1.52</td>
<td>3.11</td>
<td>0.97</td>
</tr>
<tr>
<td>Adaptation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Proprioceptive Mapping

Vector Correlation. We first quantified the degree of similarity between the patterns of errors across the three PM sessions for each subject by using a vector field correlation method. Table 4.2 shows the mean and standard deviation for the unsigned values of ρ, θ, β, for each of the three comparisons across subjects. Circular statistics were used to obtain the mean and standard deviation of θ (Berens, 2009). First, we compared the P1 vector field with that of P2. Since these two maps served as baselines, we were expecting them to be stable and thus highly correlated. Table 4.2 shows the correlation coefficient, scaling factor, and angle of rotation for the comparison between P1 and P2. These results indicate that these two baseline maps are as stable as we have previously reported. However, the comparisons between each of the baselines with the post PA map (P1 vs. P3 and P2 vs. P3) also turned out to be as correlated. These results suggest that all the maps were as stable or even more stable as previously reported. Moreover, these results indicate that the vector correlation method might not be sensitive enough to probe the effect of VA on the map. Therefore, we decided to use other methods not previously used by us to analyze these data.
Table 4.2

Test of Similarity Across Proprioceptive Mapping Sessions: Resulting in $\rho$, $\theta$, $\beta$ from the Vector Field Correlation Analysis of the Estimation Errors.

<table>
<thead>
<tr>
<th></th>
<th>$\rho$</th>
<th>$\beta$</th>
<th>$\theta$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td>P1-P2</td>
<td>.64</td>
<td>.07</td>
<td>.64</td>
</tr>
<tr>
<td>P1-P3</td>
<td>.51</td>
<td>.11</td>
<td>.45</td>
</tr>
<tr>
<td>P2-P3</td>
<td>.74</td>
<td>.06</td>
<td>.69</td>
</tr>
</tbody>
</table>

*Note.* M=Mean. SD=Standard deviation. $\theta$, angles in degrees.

Effect of Visuomotor Adaptation on the proprioceptive mapping.

**Mean magnitude of the estimation errors.** To determine if the visuomotor perturbation had an effect on the magnitude of the errors, we performed a three time (proprioceptive maps before and after VA: P1, P2, P3) x target location (16 targets) repeated-measures analysis of variance (RM-ANOVA). We carried this analysis for each subject separately due to the idiosyncrasies in the maps. In addition, this subject-specific analysis allowed us to investigate the subject-specific pattern of generalization. Table 4.3 shows the results of the RM-ANOVA across PM sessions and target locations and the corresponding post hoc tests for each of the subjects. The analyses revealed a significant effect on the magnitude of the errors across PM sessions for four of the subjects. The post hoc test using the Bonferroni correction revealed that the magnitude of the errors increased after the perturbation: from P1 to P3 for four subjects and from P2 to P3 for two...
subjects. However, there was a significant change in the magnitude of the errors across baselines for three of the subjects. These results indicate that the perturbation had an effect on the mean magnitude of the errors when the target locations were pooled together. The one subject who did not have a significant effect of the proprioceptive mapping sessions had the smallest adaptation to the perturbation: 1.7cm (see Table 4.1).

Table 4.3

Mean Error Magnitude: Single-Subject Repeated-Measures ANOVA

Comparing Proprioceptive Sessions and Target Location

<table>
<thead>
<tr>
<th>Source</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Sessions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$F(2,126)$</td>
</tr>
<tr>
<td></td>
<td>= 10.47</td>
</tr>
<tr>
<td></td>
<td>$p &lt; .0001^{**}$</td>
</tr>
<tr>
<td>P1</td>
<td>7.49 +/- .39</td>
</tr>
<tr>
<td>P2</td>
<td>5.72 +/- .34</td>
</tr>
<tr>
<td>P3</td>
<td>9.53 +/- .40</td>
</tr>
<tr>
<td>P1 vs P2</td>
<td>$p = .012^{*}$</td>
</tr>
<tr>
<td>P1 vs P3</td>
<td>$p = .0002^{**}$</td>
</tr>
<tr>
<td>P2 vs P3</td>
<td>$p = .250$</td>
</tr>
<tr>
<td>Target</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$F(15,63)$</td>
</tr>
<tr>
<td></td>
<td>= 5.2,</td>
</tr>
<tr>
<td></td>
<td>$p &lt; .000^{**}$</td>
</tr>
<tr>
<td>Sessions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$F(30,126)$</td>
</tr>
<tr>
<td>X</td>
<td>= 1.82</td>
</tr>
</tbody>
</table>

105
To determine if the visuomotor perturbation had an effect on the magnitude of the errors at the spatial location of the perturbation (target # 15) and at any other target location of the proprioceptive map, we performed separate RM-ANOVAs for each target location across the three proprioceptive sessions. Since the previous analysis revealed a significant interaction between proprioceptive mapping session and target location for four subjects (see table 4.3: last row for the first four subjects), we furthered explored the effect of VA on target location for only these four subjects. The results of the analysis revealed that the perturbed target (target # 15) did not significantly change across PM sessions for any subject. Nonetheless, there were statistically significant changes observed at other target locations. For subject # 1, we observed a significant increase of the magnitude of the errors from P1 to P3 at target # 3 ($p = .005$) and from P1 to P2 at target # 9 ($p = .02$). For subject # 2, we observed a significant increase of the magnitude of the errors from P1 to P2 and from P1 to P3 at target # 6 ($p = .001$, $p = .003$). For subject # 3, we observed a significant increase of the magnitude of the errors from P1 to P2 at target # 1 ($p = .008$), from P1 to P2 and from P1 to P3 at target # 3 ($p = .017$, $p = .008$), from P1 to P3 at target # 8 ($p = .009$), from P2 to P3 at target # 9 ($p = .004$), and from P2 to P3 at target # 10 ($p = .033$). However, all the $p$-values above .003 were not considered statistically significant after correcting for multiple comparisons. These results indicate

<table>
<thead>
<tr>
<th>Target</th>
<th>$p = .012^*$</th>
<th>$p = .030^*$</th>
<th>$p &lt; .0001^{**}$</th>
<th>$p = .042^*$</th>
<th>$p = .067^f$</th>
</tr>
</thead>
</table>

*Note.† Greenhouse-Geisser corrected, $^*p < .05$, $^{**}p < .01$*
that the magnitude of the errors rarely changed across proprioceptive sessions, as only 1 out of 240 comparisons were significant.

In addition, target location had a significant effect on the magnitude of the errors for each of the 5 subjects (see table 4.3), which indicates that the magnitude of the errors varied across the workspace. Although we aimed to test our hypothesis that there were areas on the map (specific target locations) that could be affected differently than others, this subject-specific analysis proved to be a challenge due to the non-uniformity of the maps. Figure 4.5 shows the mean error as a function of target location for all the subjects as well as for the pooled data across subjects. This figure shows that the pattern of the magnitude of errors varied across target locations for each map, which is in agreement with our previously reported finding that these maps are non-uniform across the workspace (Chapter Two). Indeed, there were significant differences in the magnitude of the error between target locations at both P1 and P2. Since P1 and P2 served as the baseline maps, finding an effect of VA on P3 became more challenging with such variation within the baselines. Indeed, we were unable to find any systematic changes on the magnitude of the error after VA.
Figure 4.5. Mean error magnitude as a function of target location for the three proprioceptive mapping sessions for each of the subjects and for the pooled data across all subjects.

To further analyze the effect of the perturbation on the magnitude of the error, we also analyzed the x and y components of the mean errors for each subject separately. To this end, we performed a three time (proprioceptive maps before and after VA: P1, P2, P3) x target location (16 targets) repeated-measures analysis of variance (RM-ANOVA) for each direction and subject separately. The results of these analyses are displayed in table 4.4. There was a significant increase in the magnitude of the x-component of the error vector for four of the subjects. Post hoc tests using the
Bonferroni correction revealed the error magnitude increased in the x-axis from P1 to P3 for three of the subjects, from P2 to P3 for two of the subjects, and from P1 to P2 for two of the subjects. There were not significant interactions between proprioceptive sessions and target location. Similarly, there was a significant increase in the magnitude of the y-component of the error vector for two of the subjects ($F(2,128) = 7.614, p = .001; F(2,128) = 3.528, p = .032$). Post hoc tests using the Bonferroni correction revealed the error magnitude increased in the y-direction from P1 to P3 and from P2 to P3 for subject #1 (4.108 +/- .279 vs 5.313 +/- .256, $p = .001$; 4.516 +/- .310 vs 5.313 +/- .256, $p = .024$) but it did not reveal significant comparisons for subject #2. There were also not significant interactions between proprioceptive sessions and target location. Taken together, these results suggest that the x-component of the error vector was more readily affected than the y-component of the error vector.
Table 4.4

X-Component of the Mean Error Vector: Single-Subject Repeated-Measures

ANOVA Comparing Proprioceptive Sessions and Target Location.

<table>
<thead>
<tr>
<th>Source</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Sessions</td>
<td>F(2,128)</td>
</tr>
<tr>
<td></td>
<td>4.94</td>
</tr>
<tr>
<td></td>
<td>p = .009**</td>
</tr>
<tr>
<td>P1</td>
<td>5.4+/- .38</td>
</tr>
<tr>
<td></td>
<td>P1 vs P2</td>
</tr>
<tr>
<td>P2</td>
<td>6.38+/- .32</td>
</tr>
<tr>
<td></td>
<td>P1 vs P3</td>
</tr>
<tr>
<td>P3</td>
<td>6.82+/- .42</td>
</tr>
<tr>
<td></td>
<td>P2 vs P3</td>
</tr>
<tr>
<td>Target</td>
<td>F(15,64)</td>
</tr>
<tr>
<td></td>
<td>6.12</td>
</tr>
<tr>
<td></td>
<td>p &lt; .0001**</td>
</tr>
<tr>
<td>Sessions</td>
<td>F(30,128)</td>
</tr>
<tr>
<td>X</td>
<td>1.68</td>
</tr>
<tr>
<td>Target</td>
<td>p = .025*</td>
</tr>
</tbody>
</table>

*p < .05, **p < .01

In addition to the single subject analysis, we also investigated the effect of the perturbation on the magnitude of the errors for the pooled data across subjects. We have previously reported that the maps were not completely idiosyncratic but that there were common themes on the structure.
of the map across subjects. Therefore, we performed the same analysis as above with the pooled data across subjects for the magnitude, x and y components of the error vector (see Figure 4.6). The analysis on the magnitude of the errors revealed a significant effect of the PM session and target location, but did not reveal significant interactions between the two (see Table 4.5).

Table 4.5

Mean Error Magnitude, Magnitude of the X- and Y-Components of the Error Vector: Repeated-Measures ANOVA Results Comparing Proprioceptive Sessions and Target Location Across Subjects.

<table>
<thead>
<tr>
<th>Source</th>
<th>Magnitude</th>
<th>X-component</th>
<th>Y-component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sessions</td>
<td>$F(1.92,766) = 8.48$</td>
<td>$F(1.92,768) = 8.23$</td>
<td>$F(2,768) = 2.83$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; .0001^{**}$</td>
<td>$p = .0003^{**}$</td>
<td>$p = .06$</td>
</tr>
<tr>
<td>P1</td>
<td>6.01$\pm$.17</td>
<td>4.10$\pm$.17</td>
<td>3.43$\pm$.13</td>
</tr>
<tr>
<td>P2</td>
<td>6.25$\pm$.17</td>
<td>4.49$\pm$.17</td>
<td>3.33$\pm$.13</td>
</tr>
<tr>
<td>P3</td>
<td>6.87$\pm$.18</td>
<td>4.97$\pm$.18</td>
<td>3.71$\pm$.15</td>
</tr>
<tr>
<td>P1 vs P2</td>
<td>$p = .798$</td>
<td>$p = .229$</td>
<td></td>
</tr>
<tr>
<td>P1 vs P3</td>
<td>$p = .001^{**}$</td>
<td>$p = .0005^{**}$</td>
<td></td>
</tr>
<tr>
<td>P2 vs P3</td>
<td>$p = .005^{**}$</td>
<td>$p = .040^{*}$</td>
<td></td>
</tr>
<tr>
<td>Target</td>
<td>$F(15,383) = 4.74$</td>
<td>$F(15,384) = 3.45$</td>
<td>$F(15,384) = 4.44$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; .0001^{**}$</td>
<td>$p &lt; .0001^{**}$</td>
<td>$p &lt; .0001^{**}$</td>
</tr>
<tr>
<td>Sessions X</td>
<td>$F(28.82,766) = 1.26$</td>
<td>$F(30,768) = 1.22$</td>
<td>$F(30,768) = .98$</td>
</tr>
<tr>
<td>Target</td>
<td>$p = .047^{†}$</td>
<td>$p = .2$</td>
<td>$p = .499$</td>
</tr>
</tbody>
</table>

$^{†}$ Greenhouse-Geisser corrected, $^{*}p < .05$, $^{**}p < .01$
Figure 4.6. Mean error magnitude, magnitude of the x- and y-components across subjects for the three proprioceptive sessions: P1, P2, and P3. Error bars represent the standard error of the mean.

Figure 4.5 (All) shows the mean error magnitude for the three PM sessions as a function of target location. It is evident from this panel that there were not specific target locations at which the mean error changed across PM sessions. On the other hand, post hoc tests using the Bonferroni correction revealed the error magnitude increased from P1 to P3 and from P2 to P3 when the target locations were pooled together. The magnitude of the change was .86 cm and .62 cm, respectively. Similarly, the analysis on the pooled data of the magnitude of the x-component of the errors revealed a significant effect of the PM session and target location (Greenhouse-Geisser corrected), but did not reveal significant interactions between the two. Post hoc tests using the Bonferroni correction revealed the error magnitude increased from P1 to P3 and from P2 to P3 (see Table 4.5). The magnitude of the change was .87 cm and .48 cm, respectively. There were not significant
effects of the target location for the y-direction of the error vector. Figure 4.6 shows the mean error across subjects for the three PM sessions and for the magnitude, x- and y- components of the error vector. In addition, the figure shows that the x-component of the error vector was larger across maps than the y-component. These results agree with the single-subject analysis and suggest that the x-component of the error vector was more readily affected than the y-component of the error vector. This conclusion is as expected since the perturbation was applied along the x-axis.

**Mean direction of the estimation errors.** To determine if the visuomotor perturbation had an effect on the direction of the errors at the spatial location of the perturbation (target # 15) and at any other target location of the proprioceptive map, we performed circular statistics to compare the direction of the 5 estimation errors (5 repetitions) at each target location for each subject separately. This resulted in 48 comparisons for each subject (P1 vs. P2, P1 vs. P3, P2 vs. P3 x 16 target locations). In specific, we used the Watson-Williams multisample test, which is the circular analogue of the one-factor ANOVA test, and then the Benjamini-Hochberg procedure to control the false discovery rate (FDR) due to the multiple comparisons. The Watson-Williams test revealed that the direction of the errors changed at the perturbation location (target # 15) only when comparing across the baseline mappings for two subjects. There was not a significant change in direction at this location after the perturbation for any of the subjects. When we performed this analysis at the other target locations, it revealed that the direction of the errors changed after VA at 3 target locations for subject # 1,
at 5 target locations for subject #2, at 3 target locations for subject #3, at 10 target locations for subject #4, and at 9 target locations for subject #5 before correcting for multiple comparisons. Similarly, the direction of errors changed between the baseline mappings for 2 target locations for subject #1, 5 target locations for subject #2, 2 target locations for subject #3, 6 target locations for subject #4, and 4 target locations for subject #5.

However, most of these significant effects were lost after correcting for multiple comparisons. After using the Benjamini-Hochberg procedure, only subjects 4 and 5 had significant changes in the direction of the errors. There was a significant change in the direction of the errors from P1 to P3 at target 10 and from P1 to P2 at target 14 \((p = .0021, p = .001)\) for subject #4, and from P1 to P3 at targets 3, 4, 6, 7, 9, 11, and 13 \((p = .009, p = .0021, p = .0031, p = .0052, p = .0042, p = .0063, p = .001)\), from P2 to P3 at target 9 \((p = .0115)\), and from P1 to P2 at targets 6, 11, and 13 \((p = .0083, p = .0073, p = .01)\) for subject #5. These results indicate that the direction of the errors rarely changed across proprioceptive sessions as only 13 out of 240 comparisons were significant and 3 out of 5 subjects didn’t have any significant changes at all.

In addition to the single subject analysis, we also investigated the effect of the perturbation on the direction of the errors for the pooled data across subjects. However, we looked at the change in mean direction instead, since the direction of the errors was not uniform across targets within each map or across subjects. Figure 4.7 displays the mean resultant vector at each target location for the three PM sessions for two exemplary subjects. Indeed,
it can be seen that the direction of the errors was not uniform across the workspace for each subject, and neither was the pattern of the direction of the errors uniform across subjects. The Watson-Williams multisample test revealed a statistically significant decrease in the angle between P2 and P3 compared to the other two angles (see table 4.6). This result suggests that visuomotor adaptation affected the mean direction of the errors in P3 compared to P2. However, it is important to note that the standard deviation of these angles was quite large.

![Figure 4.7](image-url)

**Figure 4.7.** Mean resultant vector at each target location for the three proprioceptive mapping sessions for two exemplary experimental subjects
Table 4.6

*Mean Direction of the Error: Pooled Data Watson-Williams Test*

<table>
<thead>
<tr>
<th>Sessions</th>
<th>P1P2 vs. P1P3</th>
<th>P1P2 vs. P2P3</th>
<th>P1P3 vs. P2P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F(1,158) = 0.28$</td>
<td>$F(1,158) = 20.74$</td>
<td>$F(1,158) = 24.31$</td>
<td></td>
</tr>
<tr>
<td>$p = .59$</td>
<td>$p = 1.05E-5**$</td>
<td>$p = 2.06E-6**$</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stats</th>
<th>P1P2</th>
<th>P1P3</th>
<th>P2P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Vector</td>
<td>67.32°</td>
<td>72.54°</td>
<td>31.91°</td>
</tr>
<tr>
<td>Circular Std dev.</td>
<td>57.77°</td>
<td>62.26°</td>
<td>37.26°</td>
</tr>
</tbody>
</table>

**$p<.01$**

*Variable Error of the estimation errors.* Finally, we investigated the amount of noise in the system by analyzing the overall variance in the workspace. To this end, we used a 3 time (proprioceptive maps before and after VA: P1, P2, P3) repeated-measures analysis of variance (RM-ANOVA).

Figure 4.8 shows the variable error on the x- and y-axis as well as the total variable error for the three PM sessions across subjects. The RM-ANOVA indicated that the variable error significantly changed across the proprioceptive sessions on the x direction ($F(2,30) = 11.836$, $p < .0001$). The pairwise comparisons revealed that the variable error in the x direction significantly increased from P1 to P2 and from P1 to P3 (21.28 +/- 1.79 vs. 32.2 +/- 3.95, $p = .024$; 21.28 +/- 1.79 vs. 38.25 +/- 4.16, $p = .001$). There were not significant effects across sessions in the y-direction. Finally, there were significant effects across sessions for the total variance ($F(2,30) = 10.75$, $p < .0001$), which increased from P1 to P3 (39.22 +/- 2.71 vs. 56.835 +/- 5.05, $p =$
To further investigate whether the variance was different in the x- or y-axis, we used an independent t-test for each proprioceptive session separately. This analysis revealed a significant difference between the variance in the x- and y-axis in P2 (32.2+/− 15.78 vs. 16.44+/− 7.6, t(21.58) = 3.599, p = .002: Welch-Satterwaite corrected) and in P3 (38.25+/− 16.63 vs. 18.58+/− 9.5, t(23.86) = 4.1, p < .0001: Welch-Satterwaite corrected). Taken together, these results suggest that the mean error was more variable along the x-axis than along the y-axis. Secondly, the results also show that the variable error was quite large. Large variance makes it difficult to see any consistent patterns or trends in the data. While the magnitude of the aftereffects was about 2.5 cm, the variance across the workspace along the x-axis after VA was 38.25 cm^2, which corresponds to a deviation of about 6 cm.

![Variable error on the x and y directions as well as the total variable error for the three proprioceptive sessions for the prism subjects](image)

*Figure 4.8. Variable error on the x and y directions as well as the total variable error for the three proprioceptive sessions for the prism subjects*
**Control for the effect of training.** To further investigate the increase of the magnitude and variance of the error across the proprioceptive mapping baselines (P1 and P2), we recruited two subjects for a control experiment. The purpose of the control study was to test whether the observed difference in the estimation errors was due to the time between the baseline sessions (3-5 days), to the training during the Reach Training with veridical feedback, or to the Reach Aftereffects 1. To this end, we had the subjects perform an experiment very similar to the one experimental subjects performed during Part 1. Figure 4.9 shows the experimental design for this control experiment. We had subjects perform P1 during the same session as to avoid having a long time interval between P1 and P2. Then, subjects performed a Reach Training task with veridical feedback followed by P2. Next, subjects performed an Aftereffect test with no visual feedback followed by the last proprioceptive mapping (P3). Finally, subjects performed another Aftereffects test with no visual feedback. Therefore, if changes were observed between P1 and P2 but not between P2 and P3 in this control experiment, then the changes observed between P1 and P2 during the experimental session could be attributed to the 50 trials of Reach training with terminal feedback (Figure 4.1). On the other hand, if changes were observed between P2 and P3 but not between P1 and P2 in this control experiment, then the changes observed between P1 and P2 during the experimental session could be attributed to Aftereffect task with no visual feedback.
Figure 4.9. Control experiments task timeline.

We measured the magnitude and variable error of the estimation errors in the same way as we did for the experimental subjects. Figures 4.10 show the mean magnitude and variance of the error for these control studies. The results of the RM-ANOVA on the magnitude of the error revealed no significant changes across PM sessions ($F(2,318) = 1.0, p = .36$). Similarly, the RM-ANOVA on x, y and total variable error did not reveal any significant changes across PM sessions (see table 4.7). These results suggest that neither the Reach Training task nor the Aftereffects task had an effect on the maps. Furthermore, this suggests that the slight difference observed in the estimation errors between P1 and P2 might be due to the time in between proprioceptive baseline sessions.
Figure 4.10. Mean error, variable error on the x and y directions as well as the total variable error for the three proprioceptive sessions for the control study.

Table 4.7

Variable Error X, Y and Total: Repeated-Measures ANOVA Results

Comparing Proprioceptive Sessions Across Subjects.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Variable Error X</th>
<th>Variable Error Y</th>
<th>Variable Error T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Subject 1</td>
<td>$F(2,30) = 1.5,$</td>
<td>$F(2,30) = 0.63,$</td>
<td>$F(2,30) = 2.1,$</td>
</tr>
<tr>
<td></td>
<td>$p = 0.25$</td>
<td>$p = 0.53$</td>
<td>$p = 0.14$</td>
</tr>
<tr>
<td>Control Subject 2</td>
<td>$F(1.4,38) = 3.67,$</td>
<td>$F(2,38) = 0.81,$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$p = 0.58$</td>
<td>$p = 0.054†$</td>
<td>$p = 0.45$</td>
</tr>
<tr>
<td>Pooled data</td>
<td>$F(1.7,70) = 1.5,$</td>
<td>$F(1.6,70) = 1.7,$</td>
<td>$F(2,70) = 1.1,$</td>
</tr>
<tr>
<td></td>
<td>$p = 0.23†$</td>
<td>$p = 0.20†$</td>
<td>$p = 0.33$</td>
</tr>
</tbody>
</table>

† Greenhouse-Geisser corrected
DISCUSSION

The goal of the present study was to determine whether localized visuomotor adaptation (VA) of the right hand led to a change in the estimation of hand location on our proprioceptive mapping task. If so, we aimed to determine whether the adaptation affected untrained areas of the workspace and if the generalization pattern was non-uniform and subject specific. To this end, we measured the estimation errors before and after visuomotor adaptation at 16 target locations across a 2-D horizontal workspace. We then analyzed the effect of the visuomotor adaptation on the direction and magnitude of the errors at a single-subject level as well as on the pooled data across subjects. Our findings suggest that VA had a significant effect on the magnitude and direction of estimation errors across subjects. The single-subject analysis revealed that neither of these metrics changed after VA at the target location that spatially matched the perturbation location but they did change at a few other target locations across the proprioceptive sessions. However, these few significant changes were not only observed after VA but across the baseline maps. Here we discuss the limitations in our experiment that might have influenced the magnitude of the observed effect.

**Single-Subject Design.** Our analysis of the estimation errors on a single-subject level probed to be challenging and yielded no significant effects. Although, it is standard in behavioral studies to pool data across subjects, this analysis is only useful when looking for general trends in the data. Here, we argue that any systematic changes in our maps are
intrinsically subject-specific. However, these single-subject analyses probed to be challenging due to the non-uniformity of the maps. Indeed, the direction and magnitude of the errors varied more across target location within a map than across maps for a target location. In fact, the VA had little effect on the maps as seen on the 160 comparisons made across the baselines and the post VA map (P1 vs. P3 and P2 vs. P3 x 16 target locations x 5 subjects), in which only 6 out of 160 comparisons resulted in a significant change in magnitude of the error and 9 out of 160 comparisons resulted in a significant change in direction of the error. Perhaps more significant differences were lost due to the multiple comparisons correction, which sometimes could be a little conservative. However, the Benjamini-Hochberg correction is known to be less conservative than the Bonferroni correction (Benjamini & Hochberg, 1995). Moreover, these corrections are necessary as the probability of type I errors increases with multiple comparisons.

Our findings revealed no effect on the direction or magnitude of the error at the perturbed target location (target # 15) for any of the subjects. This finding is especially intriguing since we did observe an overall effect of VA on the proprioceptive map when we pooled the data across subjects. Based on our hypothesis that there are areas on the workspace that are more stable than others, it is entirely possible that the perturbed target location was stable and robust to the perturbation but other target locations were not. This highlights a possible flaw on our methodological design, in which it could have been possible to tailor the location of the perturbation for each subject. This subject-specific perturbation could have been possible since we
captured the first baseline map a few days before the experimental session took place. To this end, we would have needed to determine what parameters constitute a stable vs. unstable target location in order to tailor the location of perturbation on the workspace. However, determining these parameters from the patterns of generalization was a goal in the present experiment.

The purpose behind choosing the perturbation location to be in the middle of the map was based on our previously published results of the non-uniformity of the map (Rincon-Gonzalez, Buneo, & Helms Tillery, 2011a; Rincon-Gonzalez, Warren, Meller, & Helms Tillery, 2011b). We had observed that across subjects, the magnitude of the errors at the middle far location were smaller than the errors at the periphery but larger than the errors at locations closer to the subjects’ body. We did not want to perturb a location at the periphery of the map where subjects might have the largest errors or close to their bodies where subjects might have the smallest errors. Similarly, since the magnitude of errors at this middle location seemed to be similar across subjects, this approach allowed us to pool the estimation errors across subjects.

**Group Design.** In addition to analyzing the effect of PA on a single subject basis, we chose to also look for generalized effects on the pooled data. We have previously argued that although the maps are idiosyncratic, there are common themes across subjects. In addition, previous studies that have found a motor learning effect on proprioception have used group designs to analyze the data (Cressman & Henriques, 2010; Ostry et al., 2010). In agreement with those studies, we observed significant differences on the
estimation errors after VA. The question that arises is why did we observe an
effect of VA on the group-design but not on the single-subject design? It could
be possible that the reason why we and other studies have observed an effect
of VA on proprioception is due to those common themes across subjects. It
follows that there could have been small effects of the adaptation on each
subjects’ maps, which were not strong enough to become significant on their
own. When we pooled the data together, those small effects could have been
amplified if they belonged to a common theme across subjects. Although we
performed single-subject analysis to identify subject-specific patterns of
adaptation across the workspace, patterns of adaptation from the pooled data
could also provide insight into those common themes on the structure of the
map. Unfortunately, there were no significant effects on the interaction
between target location and proprioceptive sessions to allow us to look
further into which target locations were affected and which ones were not.

**Generalization.** Even though we were unable to find which specific
target locations were affected by the perturbation or where in the map the
pooled effect came from, it might be possible that the effect of the
perturbation generalized to weaker areas of the map. If this were the case,
then this result suggests that the internal representation used to estimate
hand location uses a more global solution than a set of local solutions, which
is in line with our hypothesis. There is currently some debate in the
literature regarding whether the pattern of generalizations is consistent with
a global or local representation. Interestingly, studies trying to solve the
debate, have suggested that the representation used during motor learning is
neither global nor local but lies somewhere in between (Ghahramani et al., 1996; Imamizu, Uno, & Kawato, 1995; Krakauer et al., 2000; Malfait et al., 2007; Shadmehr & Mussa-Ivaldi, 1994). These studies argued that the learning was not local due to the observed generalization to untrained areas of the workspace. On the other hand, because the patterns of generalization were not uniform and tended to decay with distance from the perturbed location, they argued that the learning was not completely global. Here, we were trying to test our hypothesis that the non-uniformity of the representation is an intrinsic part of it and thus does not imply that the solution used is not global.

**Direction of the Effect.** Furthermore, our analysis of the x- and y-components of the error vector agrees with our findings of the overall VA effect on the proprioceptive map. Our results revealed that the visuomotor perturbation only affected the x-component of the vector error after VA, which matches the axis of the perturbation. Indeed, the observed effect could be a result of the direction of the perturbation, which agrees with other studies where the change in sensory recalibration was in the same direction as subjects adapted their reaches (Cressman, Salomonczyk, & Henriques, 2010; Ghahramani et al., 1996; Ostry et al., 2010). Moreover, the observed effect could be due to the fact that perturbations to the x-axis are more sensitive than perturbations to the y-axis. Ghahramani’s (1996) results revealed that the one-point x perturbation resulted in larger adaptation than the one-point y perturbation (Ghahramani et al., 1996). Thus, it is possible that the effect in our study generalized more easily on the x direction.
Contrary to these studies, we could not confirm if the effect was on the same direction (left) as the perturbation. This is mostly due to the variability of the direction of the errors, in which the mean direction of the error was different at each target location across the workspace.

**Magnitude of the Effect.** It is evident that the observed perturbation effect on the estimation of the errors was not strong enough to allow us to test our hypotheses. We will now discuss two possibilities for this result. First, it is possible that any systematic patterns of adaptation were lost on the variability of the estimations because the magnitude of the perturbation was smaller than the variance in the error. Second, it is also possible that the visuomotor adaptation was not the adequate tool to test our hypotheses.

**Variable Error.** Even though our findings suggest a VA effect on the estimation of the errors, we were unable to find a systematic change that would provide insight into the non-uniform stability of the proprioceptive map. We believe that this systematic effect was lost in the inherent variance of the estimations.

Our findings show that the estimation of hand location was quite variable between trials, which was expected from the sensory uncertainty that accompanies proprioception. In agreement with van beers et al., our results show that proprioception was less precise and thus more variable in the azimuth (x-component) than in depth (y-component) of the workspace (van Beers et al., 1998). In addition, their observed variance during estimation of hand location was similar to ours: $\sim 20 \text{cm}^2$ for the x-component
of the error vector. However, our findings indicated that this variance changed across proprioceptive sessions. Since the variance increased from P1 to P2, we conducted control experiment to figure out the source of this effect. Results from the control studies revealed the variance did not significantly change across PM sessions for the control subjects. It is possible then that the observed increase between baseline sessions for the experimental subjects was due to the time gap between sessions, to the compound effect of reaching during the Reach Training and Aftereffects tasks, or due to sensory uncertainty in the estimations. We argue that it is probably the sensory uncertainty in estimating hand location, which results in large variability. This is especially true in our proprioceptive task, which required subjects to rely on a proprioceptive estimate from memory and transform that memory into a visual reference frame before the subjects could verbally indicate the location of where the hand had just been. Additionally, this uncertainty in estimating hand location could have been amplified due to motor noise. It has been reported that spindle sensitivity varies with kinesthetic demands and is sensitive to motor noise (Scheidt, Lillis, & Emerson, 2010; Slifkin & Newell, 2000), because spindle afferent signals are mediated by alpha-gamma coactivation during active movement (Ribot-Ciscar, Rossi-Durand, & Roll, 2000). Therefore, it is possible that subjects’ active reaching during the VR tasks increased the motor noise, which in turn increased the proprioceptive uncertainty. In our task, subjects reported arm tiredness after the VR tasks, which could have increased the motor noise. Finally, the reason why this
effect is only observed on the x-component is probably due to the low precision of proprioception along the azimuth.

In addition, our analysis of the variable error also suggested that the variance in the estimation of hand location was quite large. The smallest variability observed was in the order of 21 cm$^2$ and 16 cm$^2$ along the x-direction and y-directions. These values roughly correspond to a deviation of about 4-4.5 cm. It is important to note that this deviation is larger than the magnitude of adaptation, which was in the order of 2.5 cm. Here we argue that a stronger and possibly systematic effect of the VA was lost in the intrinsic variability.

**Magnitude of Proprioceptive Change.** Although visuomotor adaptation paradigms have been used to affect proprioception, the amount that proprioception changed was relatively small. For example, Cressman observed a proprioceptive change of 19-25% (~1cm) of the magnitude of the perturbation (4 cm) applied during visuomotor adaptation (Cressman & Henriques, 2009; 2010) while Ostry (2010) observed a 11-33% proprioceptive change of the estimated magnitude of the applied force field (Ostry et al., 2010). Although small, these changes in proprioception are relatively easy to quantify with their measure of proprioceptive change. These studies used a perceptual test to measure the sensed position of the subjects’ hand, where subjects were required to compare the felt position of their hand with that of the other hand or of a reference marker and determine if their right hand was to the right or left of the reference. The advantage of this method is that the binary measure (right or left) doesn’t carry over the sensory uncertainty
of hand location estimation. Therefore, visuomotor adaptation might not provide a strong enough adaptation to overcome the noise in our method for estimating hand location. In addition, visuomotor adaptation studies do not result in a complete adaptation to the perturbation. We reported that subjects adapted 50% to the perturbation, which is in agreement with other visuomotor studies that have reported incomplete adaptation to the perturbation (Cressman & Henriques, 2009: 2010; Krakauer et al., 2000).

**Limitations with Experimental Setup.** A possible explanation for the small magnitude of adaptation observed in this study is the type of visual feedback and context of the adaptation in our study. Some studies have suggested that adaptation mechanisms depend on the form of visual feedback provided during the adaptation (Clower & Boussaoud, 2000; Norris, Greger, Martin, & Thach, 2001). These studies compared the use of actual feedback of the hand with that of a computer generated representational feedback when subjects were exposed to displacing prisms. Clower and Boussaoud (2000) showed that actual feedback of the hand resulted in larger aftereffects compared to the computer generated feedback, even though the orientation of the computer screen was parallel to the table and thus on same plane of the hand. Moreover, Norris (2001) went a step further by also investigating the effect of the screen orientation and transfer across visual feedback conditions. His group found that the magnitude of aftereffects was greater with actual feedback, compared to when the subjects saw a video of their actual hand or a cursor representing their hand on a vertical computer screen. In addition, the largest carryover of prism effects was observed from
actual feedback to either of the two other conditions, while carryover after video feedback was significantly smaller, and carryover after cursor feedback was almost undetectable. Taken together, these results suggest that discordance between actual limb position and visual feedback about limb position can affect the process of adaptation. Therefore, the discordance between the workspace and the cursor feedback in our experiment might have resulted in smaller adaptation errors.

The justification for the observed difference on those studies comes from the object unity assumption, which states that the information obtained from different senses and thus different intrinsic spatial representations come from the same event in extrinsic space (Bedford, 1999; Held, a, & Greene, 1966; Radeau & Bertelson, 1977; Welch, 1994; Welch & Warren, 1980). If this assumption is not met, then the aftereffects may reflect strategic recalibration instead of spatial realignment (Redding et al., 2005). Since this assumption was violated on our experiments, it can be possible that subjects used a strategic control to adapt to the perturbation and thus proprioception was not realigned. Strategic control refers to a process of calibrating the proprioception-motor reference frame for the specific task while realignment refers to the transformation between visual-motor and proprioceptive-motor coordinates (Redding et al., 2005). Therefore, it is possible that subjects in our task used a task-specific adaptation that did not translate completely to the proprioceptive mapping workspace.

Finally, another limitation on the study was the time in between the two sessions. Our observations suggest that the subjects’ estimations were
more similar during the second session compared to the first session. In other words, the pattern of errors changed more between the two experimental sessions (P1 vs. P2 and P1 vs. P3) than between the two proprioceptive sessions (P2 vs. P3) performed during the last experimental session. This observation was true for the variable error and for the direction of the error analysis. The change in variable error along the x-axis was smallest between P2 and P3. Similarly, the circular mean and standard deviation of the angles between P2 and P3 was smaller than the circular mean and standard deviation for the angles between P1 and P2 as well as for between P1 and P3. In addition, the results of our control studies suggested that the changes observed between the baseline measures could have been due to the time in between sessions.

**Conclusion.** In conclusion, we cannot adequately address our questions before we can reduce the noise in the system by performing all the proprioceptive sessions during the same experimental sessions. In addition, we need to be certain that the magnitude of the adaptation is greater than the intrinsic noise in the system and that we are not inducing a task-specific strategy during the adaptation. To this end, we propose that prism adaptation might be an adequate way to test our hypothesis. Prism adaptation is known to create a global realignment of the visual-motor and proprioceptive-motor internal coordinates and to result in large aftereffects (Redding et al., 2005). Moreover, prism adaptation readily generalizes to other contexts (Redding & Wallace, 2006). Thus, a strong and global perturbation would allow us to test our hypothesis that the calibration of the
internal representation of hand location is non-uniform across the workspace, which will have areas that are more robust than others to the perturbation.
Chapter 5

PRISM ADAPTATION STUDY

INTRODUCTION

Our sense of limb position, a fundamental proprioceptive process, is crucial for movement control and interacting with the environment. For proprioception to support these actions, there has to be an internal representation of the body parts in space. Evidence from this comes from computational studies on sensorimotor integration that suggest that instead of using a single perceptual and motor snapshot to provide information about the current state of both the world and one’s own body, an internal estimate of this state is maintained and updated by current sensory and motor signals (Wolpert et al., 1995; 1998). This suggests that there is an internal representation of our body parts in space and that this representation is continuously being calibrated based on incoming sensory and motor signals. Since relatively little is known about the structure of this representation, here we aimed to provide insight into this structure by probing its calibration and stability.

We have previously shown that the internal representation of arm location can be studied through the analysis of the spatial structure of estimation errors in our proprioceptive estimation task (Chapter Two). In a set of experiments, we analyzed and reconstructed the pattern of estimation errors that resulted when subjects estimated the location of their unseen hand across a 2-D workspace (Rincon-Gonzalez, Buneo, & Helms Tillery, 2011a). Our analyses of the structure have confirmed observations (L. E.
Brown, 2003; L. E. Brown et al., 2003; Desmurget et al., 2000; Haggard et al., 2000; Helms Tillery et al., 1994; Smeets et al., 2006; van Beers et al., 1996; 1998; Vindras et al., 1998; Wann & Ibrahim, 1992) that these errors are remarkably stable, symmetric across the hands, and subject specific. In agreement with other studies (Fuentes & Bastian, 2010; Helms Tillery et al., 1994; van Beers et al., 1998; 2002; Wilson et al., 2010), our results also showed that on average subjects’ estimations are non-uniform across the workspace: errors are smallest when targets are located closer to the body. However, at the single subject level we observed that the workspace locations for the minimum and maximum estimation errors were distributed differently across subjects.

Taken together, our previous results suggest that the observed spatial structure of the pattern of errors is constructed using one global and stable solution that is being continuously calibrated non-uniformly across the workspace. The idiosyncrasy in the pattern of errors shapes the entire spatial structure and not just the larger errors at the periphery, which one might expect in the case of a set of local solutions. The idiosyncrasy of the spatial structure of the pattern of errors suggests that each individual’s internal mapping is uniquely constructed through a learning mechanism and thus it is the result of individual experience. The observed common themes on the structure of the map suggest that the spatial structure of estimation errors is a consequence of a system that is continually calibrating the proprioceptive representation of hand location. The area where we get the greatest amount of exposure is where the calibration will be best. Therefore we seek to
determine if we can perturb the stability of the structure of the proprioceptive map of hand location and whether the effect of the perturbation varies across the workspace. To this end, we propose to perturb this structure in order to analyze the resulting pattern of adaptation. We hypothesize that if we can perturb the proprioceptive map, we will observe a non-uniform pattern of adaption, in which some areas on the workspace will be more robust to the perturbation than other areas.

We have previously attempted to test this hypothesis by inducing a localized perturbation into the proprioceptive map with a visuomotor adaptation task (Chapter Four). Although we observed an effect of the perturbation on the magnitude of the errors when averaged across the workspace, we were unable to find effects at specific target locations and thus could not test our hypothesis. We suggested that the induced adaptation might have not being strong enough for the effect to leap out of the noise in the system. One possibility for this was that we did not induce a big enough adaptation with our 5 cm perturbation. Studies have shown that subjects adapt their reaches to a percentage of the visuomotor perturbation, and then proprioception is only affected by a small percentage of this adaptation (Cressman & Henriques, 2009; 2010). In addition, some studies have suggested that adaptation mechanisms depend on the form of visual feedback provided during the adaptation (Clower & Boussaoud, 2000; Norris et al., 2001), and thus discordance between actual limb position and visual feedback about limb position can decrease the effect of adaptation. In our experiment, we provided visual feedback of the location of the arm during the adaptation.
in the form of a cursor shown in an upright computer screen. Finally, visuomotor adaptation is known to have limited and complex patterns of generalization (Ghahramani et al., 1996; Krakauer, Mazzoni, Ghazizadeh, Ravindran, & Shadmehr, 2006). To address these issues, we propose that prism adaptation might be an adequate way to test our hypothesis.

Prism adaptation is known to create a global realignment of the visual-motor and proprioceptive-motor internal coordinates and to result in large aftereffects (Redding et al., 2005). Although subjects do not adapt completely to the prism perturbation and only show about 20-40% of proprioceptive recalibration (Fortis, Goedert, & Barrett, 2011; Harris, 1963; Redding & Wallace, 1994; 1997; 2000; Welch, Choe, & Heinrich, 1974), the magnitude of the induced perturbation can be easily increased with prisms than with a visuomotor adaptation. The magnitude of the perturbation depends on the distance between the target and the eyes when wearing the prism goggles. Thus a 11.4° displacing prism goggles can induce a perturbation of about 20 cm if the target is located 100 cm away from the subject’s eyes. Moreover, prism adaptation generalizes beyond exposure conditions (Alexander, Flodin, & Marigold, 2011; Bedford, 1993; 1999; Redding et al., 2005; Redding & Wallace, 2006) but only for tasks that implicate the realigned sensory-motor reference frames (Bedford, 1993; Guigon & Baraduc, 2002; Redding & Wallace, 1997). Thus, a strong and global perturbation would allow us to test our hypothesis that the calibration of the internal representation of hand location is non-uniform across the
workspace, which will have areas that are more robust than others to the perturbation.

In the present study, we have examined the effect of prism adaptation on the pattern of errors that resulted when subjects estimated the location of their unseen arm in a 2-D workspace composed of 16 target locations. The direction and magnitude of the estimation errors were assessed before and after exposure to prism goggles. Different measures were taken to ensure that prism adaptation affected the limb position sense (proprioceptive adaptation) more than the eye position sense (visual adaptation) and that perturbation induced spatial realignment and not just a strategic remapping (conscious correction). During exposure, subjects were asked to make pointing movements to a target located 100 cm in front of them as fast as they could since small movement duration has been liked to a larger adaptation to the limb position sense (Redding & Wallace, 1994). Subjects were not allowed to see their hand at the resting position but were allowed to see most of their arm once the reaching movement had started. Studies have shown that nonvisible starting positions enable misalignment detection and the consequent realignment while visible starting positions enables control strategies that result in small aftereffects (Redding & Wallace, 1997). In addition, early visual feedback of the limb results in larger proprioceptive aftereffects while terminal feedback of the limb during adaptation results in larger visual aftereffects (Redding & Wallace, 2011).
METHODS

Subjects. Fourteen [mean age: 25.8 yrs] students from Arizona State University participated in the experiment; five males and five females received the perturbation, while 2 males and 2 females served as controls for the effect of training without prism glasses. Only subjects who did not need correcting glasses (contacts were acceptable), and who verbally stated being right-handed and free of any history of visual, sensorimotor or neurological conditions were recruited. All subjects signed written informed consent documents before each experiment. The Institutional Review Board at Arizona State University approved this study.

Figure 5.1. Experimental tasks. Schematic showing the order in which the different tasks were completed. The first part of the session provided baseline measures of performance. The second part of the session consisted on the perturbation and post perturbation measures of performance.

General Experimental Setup and Procedures. There were two separate setups used during an experiment that were located next to each other in the same room. The experimental room was equipped with a motion capture system (3 Optotrack 3020 camera bars, Northern Digital Inc) to record arm movements. For all subjects, the experiment was completed in the
same day in about 1 hour, which consisted on two baseline proprioceptive mapping (PM) sessions (12 min each), pre prism adaptation tests (~2 min each), prism adaption (PA) session (5 min), post prism proprioceptive mapping (PM) session (12 min), and post prism adaption tests (~2 min each), as seen in figure 5.1. The first two PM, P1 and P2, served as baseline measurements. In addition, P2 was also used to address any changes due to the pre PA tests. The third PM, P3, came right after the prism exposure to maximize the effect of the perturbation in case it decayed overtime. Post PA tests came last as a measure of the aftereffects. If any effects were seen during these post tests, even after P3, then subjects were indeed adapted to the shift during P3. Lastly, the aftereffects test came last to provide a measurement of how much the adaptation had decayed since exposure.

Upon arriving to the laboratory, subjects were informed that their perceptual and motor coordination was going to be tested before and after pointing experiments. Then, they received a brief description of the proprioceptive mapping (PM) and prism adaptation (PA) tests, without actually telling them about the perturbation.

Proprioceptive Setup and Procedures. The estimation task setup is illustrated in figure 5.2, and is similar to that used in Rincon-Gonzalez et al. (2011) (Rincon-Gonzalez, Buneo, & Helms Tillery, 2011a). This set up consisted on a board with a color-printed grid, marked with A through K rows and 1 through 18 columns. Each square on the grid was 5 by 5 cm and had four colored targets (0.7 cm in diameter) located 1.25 cm from the edges of each square and 2.5 cm from each other along the horizontal (x)
and depth (y) directions, resulting in 766 targets. The grid dimensions were 90 cm in the x direction and 50 cm in the y direction, but because of curvature, at the midline (x = 45 cm) the depth of the grid was 55 cm.

**Figure 5.2.** Estimation task setup. This setup consisted on a board with a color-printed grid, marked with A through K rows and 1 through 18 columns. Each square had four colored targets. Also shown here are the 16 target locations used.

Subjects sat 10 cm in front of the grid, making sure their midline was aligned to the grid’s midline, which corresponded to the line between 9 and 10 (x = 45 cm). Subjects were instructed to sit straight and to keep their backs against the chair’s backrest and their left hand on their laps. Subjects wore plastic glasses designed to block the lower visual hemifield in order to prevent the subjects from seeing their right hand while at the resting position but without affecting the view of the grid. During an experiment, the experimenter stood to the right of the subject holding the subjects right wrist.
with her left hand for the duration of a session. The resting position consisted on the experimenter holding the subject’s hand behind the experimenter’s back, which resulted in the subject’s arm to be comfortably extended behind and to the right of their backs. This position also prevented the subject from seeing his or her hand, which was only paramount after prism adaptation but was done before prism adaption for consistency purposes. Before the session started, subjects were instructed to keep their eyes closed at all times while their arm was being moved and to only open their eyes when their arm was back at the resting position, at which point they could verbally report the target location of where they thought their hand had been previously at. They were asked to keep their hands in a pointing position with the right index finger extended throughout the PM session. Before the session started, subjects were shown how the experimenter was going to position their pointing finger above a target during each trial.

On each trial, the experimenter passively moved the subject’s hand from the resting position to a target where the index fingertip was held 2 cm above the target for about 5 sec before returning to the resting position. At this point, subjects opened their eyes to report the previously held position of their hands by using the column letters, row numbers, and target colors. Subjects responses were recorded to be transcribed later, and so were asked to speak loud and clear and to use a standard military alphabet to describe the column letters. For example, a subject would report a target location by saying “alpha two blue.” Subjects never received feedback as to the correct location of the target. There were three PM sessions, with 64 trials each.
Each session consisted of 4 repetitions to the same 16 targets, which were evenly spaced throughout the reachable workspace (see figure 5.2). The targets were semi-randomly presented to all subjects such that all 16 targets were randomly presented before any of them were repeated. The same target set was used in the same order for all subjects. All of the trials were performed by the same experimenter, who strove to keep the passive displacement constant and without significant change between trials and sessions. No specific path or trajectory was used to move the hand to and from the target.

**Prism Adaptation Setup and Procedures.** The setup for the perturbation was inspired and motivated by the setup and protocol used by Redding and Wallace on their many prism adaptation studies (Redding et al., 2005; Redding & Wallace, 1994; 1996; 2003). Our apparatus consisted on a table and moving-target setup located in the middle of the room surrounded by 3 Optotrack 3020 camera bars, which were set up to have unobstructed view of the subject, table, and moving-target setup. On the table, there was a black board (x: 89.6 cm; y: 55.11 cm) that operated as the first level of the apparatus. A black shelf (x: 74.17 cm; y: 27.51 cm; height: 24.95 cm), open on all sides, sat on the black board acting as the second level (see figure 5.3). The shelf protruded 12.4 cm beyond the edge of the table towards the subject. A chin rest was attached to the shelf at the center of the edge closer to the subject. The purpose of the shelf was to prevent the subjects’ view of their hand at the initial position. The initial position consisted of a modeling clay cube (2 x 2 x 2 cm^2), which subjects used to rest their right index finger. It
was located on the first level at the midline of the black board and thus aligned to the chin rest, which was located 26.64 cm away on the y-direction. A room divider (155 cm x 155 cm), stood up parallel to the table and in front of the subject, 101.94 cm away from the chin rest on the y-direction. A curtain track rail (140 cm long) was attached to the divider on the side facing the subject at 20 cm higher than the height of the table and parallel to the floor. The movable-target used for prism tests and adaptation was attached to this divider by a curtain track glider.

Figure 5.3. Prism perturbation setup. (A) This panel shows the apparatus used during the prism tasks. Subjects sat in front of the table with their head constrained by a chinrest. The initial hand position is shown here as a block under the shelf. (B) This panel shows the pointing movements made during some of the prism tasks in the absence of the prism distortion. At the initial position, subject’s arm was under the shelf and thus out of the subjects view. (C) This panel shows the pointing movements before the perturbation (solid extended arm) and at the end of the exposure task (dashed extended arm).

Subjects sat in a chair before the apparatus, with their head positioned on the chin rest, which could be adjusted to account for different subjects’ heights. Subjects were asked to keep head movements to a
minimum. During pre and post PA tests, subjects kept on wearing the plastic glasses. A motion-tracking marker was attached to the nose bridge of the glasses to keep track of head movement and subjects’ eye level. Similarly, another marker was attached to right index fingernail to record the finger trajectory to and from the initial position; the marker was taken off during PM sessions. During the PA phase, subjects performed three pre adaptation tests, a prism exposure test, three post adaptation tests, and an after effect test (see Figure 5.1). The order of the pre and post adaptation tests was randomly assigned to each subject. These tests were: hand-head proprioceptive test (PT), Eye-head visual test (VT), and eye-hand visual-proprioceptive test (V-PT). All pre and post adaptation tests were performed under very low lighting. Before each test, subjects were given a brief description of the tests to be performed and told to keep their left hand on their laps and their right index finger on the initial position with the right index finger extended at all times while resting and in between pointing movements.

The PT test required subjects to point to their perceived midline with eyes closed. They were asked to point straight ahead by extending their arm completely to a position in space believed to be aligned with their nose or midline without making any corrective movements. Subjects completed 10 out-and-back movements, at a slow and controlled rate. Any differences in performance on this test after prism exposure can be attributed to an adaptation in the limb position sense since there was no visual feedback.
In the VT, subjects were required not to move their hands from their initial positions. Subjects were asked to verbally indicate when the moving target appeared to be straight ahead of their nose. As explained before, the moving target was attached to the curtain track on the room divider, which was completely covered with a black sheet. The subjects were only able to see the curtain track and the target on the very low lighting conditions. The target consisted of one of the motion tracking markers (1.65 cm diameter), which was attached to a curtain track glider, as well as to a thin cord that went around the divider and back to the target. The experimenter was able to slide the target back and forth horizontally, by pulling on the cord while standing behind the divider and out of the subject’s view. On each trial, subjects were asked to close their eyes while the experimenter positioned the target on either the right or left side of the track at a random initial location within each side so subjects could not calculate the distance from the center to the starting position. Then, the subject was asked to open their eyes and to say stop when the target was aligned to their midline. In the meantime, the experimenter moved the target on a lateral fashion across the subjects’ visual field at different velocities each trial, which prevented the subject from calculating the distance it took the target to travel from initial position to the center by paying attention to its velocity. The target’s initial position was alternated between the right and left visual fields with a total of 8-10 trials. Any differences in performance on this test after prism exposure can be attributed to an adaptation in the eye position sense since there were no arm movements.
The V-PT required subjects to point straight ahead to the visible target, hanging from the curtain track, with their non-visible right arm while keeping their eyes open. A removable thin but sturdy black cardboard was attached to the shelf to block the subjects’ view of their moving arm while allowing them to see the target. In this case, the target was positioned straight ahead of the subjects’ midline and left on that position throughout the test. Subjects completed 10 out-and-back movements, at a slow and controlled rate. Any differences in performance on this test after prism exposure can be attributed to an adaptation in both the limb and eye position senses since there was visual feedback of the target as well as arm movements to the target.

After the pre prism adaptation tests were completed, subjects were escorted back to the PM table for the second baseline session. After finishing the PM experiment, subjects came back to the PA table. Once sited before the PA setup, the subjects traded the plastic glasses for prisms glasses (20 diopter base right, 11.4 arc degrees leftward displacement), which also had a marker attached to the right side of the frame. The lights were turn on during prism adaptation, which allowed subject to fully see their moving arm. Since the initial position was located under the shelf and chin rest, subjects were not able to see their hand at the initial location but were able to see most of their arm once the movement had started (see Figure 5.3A). Subjects were told to point with the visible hand towards the visible target located straight ahead of the chinrest by making fast ballistic movements as accurately as the could but not to make any online corrections. The subjects
were given 5 minutes to make as many pointing movements as they could. If they got tired, they were asked to rest for as long as necessary at the resting position in between movements instead of making slower movements. For the control group, subjects followed the same protocol but wore the plastic glasses instead of the prism glasses.

After the prism exposure was completed, the subject was asked to keep his/her hand out of view under the shelf while the prism glasses were exchanged for the plastic glasses. Then, subjects were asked to either keep their eyes closed or to keep their right hands behind their backs while escorted back to the PM table for the last session. View of their hand was avoided throughout the PM test post PA. After finishing the PM experiment, subjects were escorted back to the PA table to perform the post prism adaptation tests. The idea was that by keeping the subjects from seeing their hand, decay or extinction of the prism adaptation was avoided or delayed. After the post PA tests, which were the same as the pre PA tests but presented in a different order, subjects performed the after effects test (AET). During this final test, subjects performed 5-10 pointing movements in the same fashion as during the prism adaptation trial: subjects were allowed to see most of their arm while pointing towards the target with fast ballistic movements as accurately as the could but without making any online corrections while the lights were ON. The purpose of this test was to have a measure of after effects from a test that was very similar to the prism exposure test.
**Analysis.**

**Prism Adaptation.** During an experiment, seven markers were used to record 3-d position data: one marker on the index finger, one marker on the frame of the glasses, three markers on the lower-right, upper-right, and upper-left corners of the black board, one on the room divider, and one served as the moving target. The marker on the finger was used to record the subjects’ terminal accuracy in pointing at the target on each trial. The completion of a movement was signaled by a brief pause of the subjects’ finger. Although subjects were asked not to make online corrections, any movement corrections made after this pause was not included in the analysis. These corrections happened only infrequently and were only present during the first few trials of both prism exposure and after effect tests. The moving target/marker was used to record the subjects’ perception of their midline during the visual test.

Prism adaptation was measured by subtracting the pre and post mean endpoints of the pointing movement in x, y, and z for the PT and V-PT. In other words, we compared box 2, part 1 with box 3, part 2 for PT, and box 4, part 1 with box 5, part 2 for V-PT (see Figure 5.1). Measurements were computed in terms of the percentage of adaptation based on the actual prism shift (11.4 deg). A 100% adaptation to the prisms was 19.76 cm when subjects’ eyes were located at 98 cm from the target, which was the average distance across subjects. Adaptation during the VT was measured by subtracting the pre and post mean x-location of the moving target. In this case, we compared boxes 3, part 1 and 4, part 2 in figure 5.1. Percent of
adaptation during prism exposure was measured as the difference between the endpoint of the very first reach and the mean endpoint of all movements (minus the first 5 trials). Similarly, percent of adaptation at after AET was measured as the difference between the endpoint of the very first reach during AET and the mean endpoint of all movements (minus the first 5 trials) during the prism exposure trials. To this end, we compared boxes 1 and 5, part 2 in figure 5.1. We also used an independent t-test to measure the effect of the adaptation on the endpoint errors across subjects at each of the PA tasks separately (Experimental x Control for PT, V-PT, VT, VTl, and VTr). For this analysis, we computed the endpoint error by subtracting each endpoint in POST from each endpoint in PRE in x, y, and z for PS and TS separately. For VS, we subtracted the mean POST endpoint from the mean PRE endpoint in x.

**Proprioceptive Mapping.** A change in the proprioceptive map was measured as the difference in performance between the baseline maps (P1, P2) and the post PA map (P3). In other words, we compared box 1 and box 5 with box 2 in figure 5.1. Performance was evaluated by measuring the direction and magnitude of the errors between the actual and estimated target locations.

**Vector Correlation.** We first quantified the degree of similarity between the patterns of errors across the three proprioceptive sessions for each subject by using a vector field correlation method (Buneo, 2011; Rincon-Gonzalez, Buneo, & Helms Tillery, 2011a). This nonparametric method involves a pairwise vector correlation between each target location across two
vector fields that takes into account the irregularities and asymmetries in the fields in order to quantify the degree of rotational or reflectional dependence and the scaling relationship between them. A correlation coefficient of 1 indicates a perfect rotational relationship, while a coefficient of -1 indicates a perfect reflectional relationship. A small angle of rotation/reflection, $\theta$, indicates that the two vector fields are minimally rotated/reflected with respect to each other. Finally, the scaling factor $\beta$ is formed from the ratio of the variances of the two sets of vectors and indicates their scaling relationship.

**Effect of Prism Adaptation on the proprioceptive mapping.**

*Mean magnitude of the estimation errors.* To determine if the adaptation to PA had an effect on the proprioceptive map, we analyzed the magnitude of the errors at each target location across the three proprioceptive mappings with a 3 time (proprioceptive maps before and after PA: P1, P2, P3) x target location (16 targets) repeated-measures analysis of variance (RM-ANOVA). Since the perturbation consisted on a shift along the x-direction only, we also analyzed the effect of the PA for the x- and y-component of the error vector. To this end, we used a 3 time (proprioceptive maps before and after VA: P1, P2, P3) x target location (16 targets) RM-ANOVA for each component separately. These analyses were performed at both the single-subject level and on the pooled data across subjects. Finally, to determine if there was a non-uniform pattern of adaptation, we performed the same RM-ANOVA across proprioceptive sessions at each target location.
separately only for the subjects who showed a significant interaction between session and target location.

*Mean direction of the estimation errors.* In addition to analyzing the effect of PA on the magnitude of the errors, we also quantified this effect on the direction of the errors across the whole workspace. However, we could not pool the errors without accounting for the non-uniformity and idiosyncrasy of the map first. To this end, we removed this non-uniformity and idiosyncrasy by looking at the *change* in angle from one map to the other at each target location instead of looking at the actual direction of the error. In other words, we found the angle between the mean estimation errors at each target location across two PMs. For example, we computed the angle formed between the mean error vector at target #5 in P1 and the mean error vector at the same target location in P2. We then analyzed those 16 changes in direction across the three PM sessions with a Watson-Williams multisample test, which is the circular analogue of the one-factor ANOVA test.

We also quantified the effect of PA on the direction of the errors at the single-subject and single-target level. To this end, we compared the angle formed between the azimuth (0°) and the vector error (see equation 1) at each target location between two PM sessions (P1 vs. P2, P1 vs. P3, P2 vs. P3). Appropriate measures were taken in the case where the x or y components of the error vector were zero or when they were negative. Then we analyzed the resulting angles with the Watson-Williams multisample test. Since there are not circular analogues of post hoc tests, we compared the angles between two PMs for each target separately, which resulted in 48 multiple comparisons for
each subject (3 statistical tests at each of the 16 target locations). As a result of the multiple comparisons, we used the Benjamini-Hochberg procedure to control the false discovery rate (FDR). First, we ranked the individual $p$-values from each of the 48 comparisons in ascending order. Then, we compared each individual $p$-value to the FDR equation (equation 2), in which $P$ corresponds to each individual $p$-value, $i$ corresponds to the ranking of each $p$-value, $m$ corresponds to the number of multiple comparisons, and $q^*$ corresponds to the $\alpha$ level at which we are controlling the probability of type I errors. Here, we set $\alpha$ to be .05.

$$\alpha = \tan^{-1}(x/y)$$  \hspace{1cm} (1) 

$$P_{(i)} \leq \frac{i}{m} q^*$$  \hspace{1cm} (2)

*Variable Error of the estimation errors.* We also established the variability in performance and the effect of the adaptation on the variable error. To this end, we performed a 4th order regression analysis on the data from each of the subjects and on the pooled data from all the subjects. The regression equations were used to compute the variable error as follows:

$$X_{fit} = x^4 + x^3y + x^2y^2 + xwy^3 + y^4 + x^3 + x^2y + xw + y^2 + x + y$$  \hspace{1cm} (3)

$$Y_{fit} = x^4 + x^3y + x^2y^2 + xwy^3 + y^4 + x^3 + x^2y + xw + y^2 + x + y$$  \hspace{1cm} (4)

$$E_{x^2} = \frac{1}{n} \sum_{i=1}^{n} (X_{data,i} - X_{fit,i})^2$$  \hspace{1cm} (5)

$$E_{y^2} = \frac{1}{n} \sum_{i=1}^{n} (Y_{data,i} - Y_{fit,i})^2$$  \hspace{1cm} (6)
We then analyzed the variance in x \( (E_{x}^2) \), y \( (E_{y}^2) \) and the total variance \( (E_{Tot}^2) \) with a 3 time ( proprioceptive maps before and after VA; P1, P2, P3) repeated-measures analysis of variance (RM-ANOVA). We also used an independent t-test between \( E_{x}^2 \) and \( E_{y}^2 \) for each proprioceptive map.

Changes in proprioceptive estimates as a function of changes in adaptation aftereffects. Finally, we wondered whether the observed change in the magnitude of the errors depended on the level of adaptation to the perturbation. To this end, we measured the changes in the magnitude of the error vector as a function of the changes in aftereffects as a percentage of the perturbation (20 cm) for each subject. For the changes in magnitude, we subtracted the mean magnitude of the error across all target locations at P3 to that of the mean between P1 and P2. For the changes in aftereffects, we used the prism aftereffects from the visual-proprioceptive test. Then, we measured the correlation between these two groups.

RESULTS

Prism Adaptation. In order to determine if prism adaptation (PA) had an effect on the proprioceptive map (PM), we first had to determine the extent to which subjects adapted to the prism exposure. Figure 5.4 shows the mean percentage adaptation measured by comparing the endpoint of the movements before and after exposure at the different PA tests for both prism and control subjects. Subjects exposed to the prism adaptation showed larger aftereffects than control subjects. For the eye-hand visual-proprioceptive test
(V-PT), experimental subjects adapted 25.5% of the induced prism shift, which corresponded to 5 cm out of the possible 19.76 cm. Similarly, experimental subjects displayed 22.8% (4.5 cm) adaptation during the hand-head proprioceptive test (PT). During the eye-head visual post test (VT), experimental subjects perceived the visual target to be 2.4 cm (12%) in the direction of the prism shift. On the contrary, control subjects had an average shift of -1.2 cm, 0.4 cm, and 0.7 cm for the V-PT, PT, and VT tests respectively. We used an independent t-test to measure the effect of the adaptation on the endpoint errors across subjects at each of the PA tasks separately (Prism x Control for PT, V-PT, VT, VTl, and VTTr). The results of the t-test are shown in table 5.1. The test revealed a significant difference between experimental and control subjects for the PT test in the x and y axis, as well as for the V-PT in the x-axis.
Figure 5.4. Prism adaptation. Percent of adaptation with respect to the expected adaptation based on the distance between target and each subject’s eyes as a function of prism tests, for both the prism and control subjects. Error bars represent the standard error of the mean.
Table 5.1

Independent *t*-test on the Effect of the Adaptation for the Endpoint Errors Across Subjects at Each of the PA Tasks Separately (Experimental x Control for PT, V-PT, VT, VTL, and VTr).

<table>
<thead>
<tr>
<th></th>
<th><em>t</em>-test</th>
<th>Prism</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>x (t(107.56) = 11.32, p &lt; .0001** )†</td>
<td>4.42+/-.35</td>
<td>-1.25+/-.36</td>
</tr>
<tr>
<td></td>
<td>y (t(124.95) = 4.25, p &lt; .0001** )†</td>
<td>.89+/-.23</td>
<td>-.38+/-.19</td>
</tr>
<tr>
<td></td>
<td>z (t(117.04) = .24, p = .81†)</td>
<td>-.73+/-.40</td>
<td>-.60+/-.37</td>
</tr>
<tr>
<td>V-PT</td>
<td>x (t(135) = 11.65, p &lt; .0001** )</td>
<td>5.16+/-.23</td>
<td>.37+/-.32</td>
</tr>
<tr>
<td></td>
<td>y (t(135) = .2, p = .84)</td>
<td>.62+/-.29</td>
<td>.72+/-.44</td>
</tr>
<tr>
<td></td>
<td>z (t(114.05) = 1.78, p = .08†)</td>
<td>-.32+/-.35</td>
<td>-1.18+/-.33</td>
</tr>
<tr>
<td>VT</td>
<td>(t(12) = .14, p = .89)</td>
<td>.95+/-.19</td>
<td>.68+/-.19</td>
</tr>
<tr>
<td></td>
<td>(t(12) = .06, p = .95)</td>
<td>.63+/-.15</td>
<td>.51+/-.53</td>
</tr>
<tr>
<td></td>
<td>(t(12) = .23, p = .82)</td>
<td>1.31+/-.26</td>
<td>.84+/-.36</td>
</tr>
</tbody>
</table>

†Levene’s Test for Equality of Variances sig. **p<.01

Indeed, subjects who wore the prism glasses followed a standard adaptation to the prism shift. Figure 5.5A displays the mean endpoint on the x-axis as a function of trial number during exposure to the prism glasses. As seen in figures 5.4 and 5.5A, the endpoint of the very first reach during prism exposure was -7.8 cm to the left of the target (or mean reach endpoint of all trials). Subjects adapted within the first 10-15 trials. Then, the very first trial during the aftereffects test when they pointed towards the same target with visual feedback of their arms was 4.6 cm in the direction of the prism shift. On the contrary, Figures 5.4 and 5.5B show that control subjects did not
experience a shift during the 5 minutes of pointing towards the target or during the aftereffects test.

**Figure 5.5.** Prism exposure. (A) End of reaches along the x-direction as a function of time during prism exposure. The zero point represents target
location. The dotted line separates the pre and post prism exposure. (B) Same as in A, but for the control subjects.

**Proprioceptive Mapping.**

**Vector Correlation.** We first quantified the degree of similarity between the patterns of errors across the three PM sessions for each subject by using a vector field correlation method. Table 5.2 shows the mean and standard deviation for the unsigned values of $\rho$, $\theta$, $\beta$, for each of the three comparisons across subjects. Circular statistics were used to obtain the mean and standard deviation of $\theta$ (Berens, 2009). First, we compared the P1 vector field with that of P2. Since these two maps served as baselines, we were expecting them to be stable and thus highly correlated. Table 5.2 shows the correlation coefficient, scaling factor, and angle of rotation for the comparison between P1 and P2. These results indicate that these two baseline maps are as stable as we have previously reported. However, the comparisons between each of the baselines with the post PA map (P1 vs. P3 and P2 vs. P3) also turned out to be as correlated. These results suggest that all the maps were as stable or even more stable as previously reported. Moreover, these results indicate that the vector correlation method might not be sensitive enough to probe the effect of PA on the map. Therefore, we decided to use other methods not previously used by us to analyze these data.
Table 5.2

*Test of Similarity Across Proprioceptive Mapping Sessions: Resulting in $\rho$, $\theta$, $\beta$ from the Vector Field Correlation Analysis of the Estimation Errors.*

<table>
<thead>
<tr>
<th></th>
<th>$\rho$ M</th>
<th>$\rho$ STD</th>
<th>$\beta$ M</th>
<th>$\beta$ STD</th>
<th>$\theta$ M</th>
<th>$\theta$ STD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prism Subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1-P2</td>
<td>.78</td>
<td>.15</td>
<td>.78</td>
<td>.12</td>
<td>6.85</td>
<td>7.08</td>
</tr>
<tr>
<td>P1-P3</td>
<td>.78</td>
<td>.12</td>
<td>.75</td>
<td>.15</td>
<td>11.91</td>
<td>8.22</td>
</tr>
<tr>
<td>P2-P3</td>
<td>.81</td>
<td>.13</td>
<td>.79</td>
<td>.20</td>
<td>14.78</td>
<td>12.81</td>
</tr>
<tr>
<td><strong>Control Subjects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1-P2</td>
<td>.85</td>
<td>.04</td>
<td>.77</td>
<td>.10</td>
<td>8.37</td>
<td>4.05</td>
</tr>
<tr>
<td>P1-P3</td>
<td>.78</td>
<td>.12</td>
<td>.69</td>
<td>.22</td>
<td>5.51</td>
<td>3.09</td>
</tr>
<tr>
<td>P2-P3</td>
<td>.83</td>
<td>.14</td>
<td>.75</td>
<td>.19</td>
<td>5.59</td>
<td>3.10</td>
</tr>
</tbody>
</table>

Note. M=Mean. STD=Standard Deviation. $\theta$: angles in degrees

**Effect of Prism Adaptation on the proprioceptive mapping.**

*Mean magnitude of the estimation errors.* To determine if the prism adaptation had an effect on the magnitude of the errors, we performed a three time (proprioceptive maps before and after PA: P1, P2, P3) x target location (16 targets) repeated-measures analysis of variance (RM-ANOVA) for the mean magnitude, x-component, and y-component of the errors on the pooled data across subjects. Figure 5.6 shows the mean error across subjects for the three PMs: P1, P2, and P3 and table 5.3 shows the results of the RM-ANOVA. For the experimental subjects, the mean magnitude of the estimation errors significantly increased after PA but did not change across the two baselines. Similarly, the x-component of the estimation errors significantly increased after PA while the y-component did not change. These results suggest that prism adaptation significantly increased the magnitude...
of the estimation errors along the x-axis, which is the same axis as the perturbation. The magnitude of the change in the magnitude of the errors was 1.23 cm from P1 to P3 and .86 cm from P2 to P3. Similarly, the magnitude of the change in the magnitude of the errors along the x-component was 1.23 cm and 1.04 cm from P1 to P3 and from P2 to P3, respectively.

![Figure 5.6](image.png)

Figure 5.6. Mean magnitude error across subjects for the three proprioceptive sessions: P1, P2, and P3, for the prism and control subjects. Error bars represent the standard error of the mean.

For the control subjects, the mean magnitude and x-component of the estimation errors only significantly increased from P1 to P2, while it did not change for P3. On the contrary, the y-component of the error was significantly higher at P2 compared to P3. Although significant, we should point out that the magnitude of the error was barely significantly higher at P2 along the x-axis ($p = .045$) and the $p$-values for the significant effects
observed on the magnitude and y-component of error were not as small as the ones observed for the prism subjects. In addition, the magnitude of the change was almost half of that observed for the prism subjects. The magnitude of the change in the magnitude of the errors was .78 cm and around .6 cm along the x- and y- components. Finally, further investigation revealed that only 2 of the 4 control subjects had a significantly higher magnitude of the error at P2 (see table 5.6).

Table 5.3

**Mean Error Magnitude, Magnitude of the X- and Y-Components of the Error Vector: Repeated-Measures ANOVA Results Comparing Proprioceptive Sessions and Target Location Across Subjects.**

<table>
<thead>
<tr>
<th>Source</th>
<th>Prism</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sessions</td>
<td>Sessions</td>
</tr>
<tr>
<td></td>
<td>$F(2,1248)$</td>
<td>$F(2,1248)$</td>
</tr>
<tr>
<td></td>
<td>= 32.28</td>
<td>= 32.28</td>
</tr>
<tr>
<td></td>
<td>$p &lt; .001**$</td>
<td>$p &lt; .001**$</td>
</tr>
<tr>
<td>P1</td>
<td>7.50+/-.15</td>
<td>5.09+/-.14</td>
</tr>
<tr>
<td></td>
<td>$p = .053$</td>
<td>$p = .052$</td>
</tr>
<tr>
<td>P2</td>
<td>7.87+/-.16</td>
<td>5.28+/-.15</td>
</tr>
<tr>
<td></td>
<td>$p = .043*$</td>
<td>$p = .052$</td>
</tr>
<tr>
<td>P3</td>
<td>8.73+/-.18</td>
<td>6.32+/-.17</td>
</tr>
<tr>
<td></td>
<td>$p = .006**$</td>
<td>$p = .052$</td>
</tr>
<tr>
<td>P1 vs P2</td>
<td>$p = .053$</td>
<td>$p = .65$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; .001**$</td>
<td>$p = .043*$</td>
</tr>
<tr>
<td>P1 vs P3</td>
<td>$p &lt; .001**$</td>
<td>$p = 1$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; .001**$</td>
<td>$p = .57$</td>
</tr>
<tr>
<td>P2 vs P3</td>
<td>$p &lt; .001**$</td>
<td>$p = .955$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; .001**$</td>
<td>$p = .66$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; .001**$</td>
<td>$p &lt; .001**$</td>
</tr>
<tr>
<td>Target</td>
<td>$F(15,624)$</td>
<td>$F(15,624)$</td>
</tr>
<tr>
<td></td>
<td>= 9.23</td>
<td>= 6.27</td>
</tr>
<tr>
<td></td>
<td>$p &lt; .001**$</td>
<td>$p &lt; .001**$</td>
</tr>
<tr>
<td>Sessions</td>
<td>$F(30,1248)$</td>
<td>$F(30,1248)$</td>
</tr>
<tr>
<td></td>
<td>= 7.04</td>
<td>= 7.04</td>
</tr>
<tr>
<td></td>
<td>$p &lt; .001**$</td>
<td>$p &lt; .001**$</td>
</tr>
<tr>
<td></td>
<td>= 2.81</td>
<td>= 2.81</td>
</tr>
<tr>
<td></td>
<td>$p &lt; .001**$</td>
<td>$p &lt; .001**$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; .001**$</td>
<td>$p &lt; .001**$</td>
</tr>
</tbody>
</table>

161
\begin{table*}[ht]
\centering
\begin{tabular}{cccccc}
X Target & = .82 & = .93 & = 1.01 & = 1.79 & = .96 & = 1.80 \\
p & = .75 & p = .58 & p = .46 & p = .007** & p = .52 & p = .007** \\
\end{tabular}
\caption{Levene's Test for Equality of Variances sig. *p<.05; **p<.01}
\end{table*}

The RM ANOVA also indicated that target location had a significant effect on the magnitude of the error. However, there was not a statistically significant effect of the interaction between target location and proprioceptive mapping sessions for the prism subjects, indicating that no specific target locations were affected by the prism adaptation. Therefore, these results indicate that the magnitude of the errors significantly varied across the workspace but did not significantly change across proprioceptive sessions at specific target locations. Figure 5.7 shows the mean error as a function of target location for 4 exemplary subjects. It is clear from this figure that the pattern of the magnitude of the errors was not uniform across the workspace. Indeed, there were significant differences in the magnitude of the error between target locations when looking at each baseline proprioceptive map separately. Since P1 and P2 served as the baseline maps, finding an effect of PA on a specific target location on P3 became more challenging with such variation in the baselines.
Figure 5.7. Mean error magnitude as a function of target location for the three proprioceptive mapping sessions. Four exemplary subjects are shown here. Error bars represent the standard error of the mean.

Since the pattern of errors was idiosyncratic, we also performed the RM-ANOVA analysis on each subject separately to see if we could find a non-uniform adaptation. Tables 5.4-5.6 show the results of these analyses on each of the 14 subjects. Only 5 subjects showed a significant effect of prism adaptation (see table 5.4 and 5.5) while 2 of the control subjects showed a significant change at P2 (see table 5.6). All subjects showed a significant change of magnitude across target locations but only 3 experimental subjects and 1 control subject showed a significant interaction between target location and proprioceptive session. RM-ANOVA across proprioceptive sessions at each of the target locations revealed a statistically change in magnitude at few target locations. Post hoc tests revealed significant effects for only 3 of
the subjects: For subject # 3, we observed a significant increase from P1 to P3 at target # 5 \( (p = .01) \); for subject # 5, we observed a significant increase from P1 to P2 at target # 3 and #8 \( (p = .006, p = .001) \); and for control subject # 3, we observed a significant increase from P1 to P3 at target # 1 \( (p = .033) \). There results suggest that the effects observed at the single target level are probably due to random variations since there were only 4 significant effects out of the possible 672 comparisons. Therefore, we were unable to find any systematic changes on the magnitude of the error after PA.

Table 5.4

Mean Error Magnitude: Single-Subject Repeated-Measures ANOVA

Comparing Proprioceptive Sessions and Target Location for Prism Subjects 1-5.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>1-CA</th>
<th>2-KA</th>
<th>3-JdlC</th>
<th>4-CR</th>
<th>5-AnM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sessions</td>
<td>( F(2,96) )</td>
<td>( F(2,96) )</td>
<td>( F(2,96) )</td>
<td>( F(2,96) )</td>
<td>( F(2,96) )</td>
</tr>
<tr>
<td></td>
<td>= 18.52</td>
<td>= 5.00</td>
<td>= 19.48</td>
<td>= 10.68</td>
<td>= 17.95</td>
</tr>
<tr>
<td></td>
<td>( p &lt; .0001^{**} )</td>
<td>( p = .009^{**} )</td>
<td>( p &lt; .0001^{**} )</td>
<td>( p &lt; .0001^{**} )</td>
<td>( p &lt; .0001^{**} )</td>
</tr>
<tr>
<td>P1</td>
<td>5.96+/-.24</td>
<td>9.02+/-.41</td>
<td>11.33+/-.35</td>
<td>9.33+/-.39</td>
<td>9.24+/-.49</td>
</tr>
<tr>
<td>P2</td>
<td>6.10+/-.32</td>
<td>8.54+/-.36</td>
<td>11.88+/-.31</td>
<td>9.76+/-.38</td>
<td>11.68+/-.35</td>
</tr>
<tr>
<td>P3</td>
<td>8.32+/-.34</td>
<td>10.24+/-.38</td>
<td>14.04+/-.36</td>
<td>11.27+/-.43</td>
<td>11.97+/-.40</td>
</tr>
<tr>
<td>P1 vs P2</td>
<td>( p = 1 )</td>
<td>( p = 1 )</td>
<td>( p = .49 )</td>
<td>( p = .97 )</td>
<td>( p &lt; .0001^{**} )</td>
</tr>
<tr>
<td>P1 vs P3</td>
<td>( p &lt; .0001^{**} )</td>
<td>( p = .14 )</td>
<td>( p &lt; .0001^{**} )</td>
<td>( p = .0002^{**} )</td>
<td>( p &lt; .0001^{**} )</td>
</tr>
<tr>
<td>P2 vs P3</td>
<td>( p &lt; .0001^{**} )</td>
<td>( p = .003^{*} )</td>
<td>( p &lt; .0001^{**} )</td>
<td>( p = .006^{**} )</td>
<td>( p = 1 )</td>
</tr>
<tr>
<td>Target</td>
<td>( F(15,48) )</td>
<td>( F(15,48) )</td>
<td>( F(15,48) )</td>
<td>( F(15,48) )</td>
<td>( F(15,48) )</td>
</tr>
<tr>
<td></td>
<td>= 6.96</td>
<td>= 6.37</td>
<td>= 21.50</td>
<td>= 9.22</td>
<td>= 10.45</td>
</tr>
</tbody>
</table>
## Table 5.5

### Mean Error Magnitude: Single-Subject Repeated-Measures ANOVA

Comparing Proprioceptive Sessions and Target Location for Prism Subjects 6-10.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Sessions</th>
<th>X</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$F(30,96)$</td>
<td>$p=.02$</td>
<td>$p=.03$</td>
</tr>
<tr>
<td>Source</td>
<td>$F(2,96)$</td>
<td>$p=.49$</td>
<td>$p=.50$</td>
</tr>
<tr>
<td>6-BW</td>
<td>$=.73$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-DF</td>
<td>$=.70$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-FdS</td>
<td>$=.96$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-LB</td>
<td>$=.52$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-AM</td>
<td>$=2.02$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>$5.94+/-.32$</td>
<td>$6.34+/-.33$</td>
<td>$5.89+/-.36$</td>
</tr>
<tr>
<td>P2</td>
<td>$5.84+/-.36$</td>
<td>$6.71+/-.28$</td>
<td>$5.37+/-.37$</td>
</tr>
<tr>
<td>P3</td>
<td>$5.42+/-.26$</td>
<td>$6.76+/-.33$</td>
<td>$6.27+/-.35$</td>
</tr>
<tr>
<td>Target</td>
<td>$F(15,48)$</td>
<td>$p=.0002$**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$=3.78$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†Levene’s Test for Equality of Variances sig. *$p<.05$; **$p<.01$
### Table 5.6

**Mean Error Magnitude: Single-Subject Repeated-Measures ANOVA**

**Comparing Proprioceptive Sessions and Target Location for Control Subjects**

<table>
<thead>
<tr>
<th>Source</th>
<th>1·GM</th>
<th>2·FM</th>
<th>3·RP</th>
<th>4·WZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sessions</td>
<td>$F(2,96)$</td>
<td>$F(2,96)$</td>
<td>$F(2,96)$</td>
<td>$F(2,96)$</td>
</tr>
<tr>
<td></td>
<td>$= 13.75$</td>
<td>$= .36$</td>
<td>$= 5.33$</td>
<td>$= 1.82$</td>
</tr>
<tr>
<td></td>
<td>$p &lt;.0001^{**}$</td>
<td>$p = .70$</td>
<td>$p = .006^{**}$</td>
<td>$p = .17$</td>
</tr>
<tr>
<td>P1</td>
<td>$5.31+/-.30$</td>
<td>$6.46+/-.33$</td>
<td>$6.64+/-.34$</td>
<td>$5.19+/-.40$</td>
</tr>
<tr>
<td>P2</td>
<td>$6.08+/-.33$</td>
<td>$6.75+/-.39$</td>
<td>$8.12+/-.39$</td>
<td>$5.79+/-.40$</td>
</tr>
<tr>
<td>P3</td>
<td>$3.89+/-.30$</td>
<td>$6.37+/-.32$</td>
<td>$8.11+/-.36$</td>
<td>$6.16+/-.40$</td>
</tr>
<tr>
<td>P1 vs P2</td>
<td>$p = .3$</td>
<td></td>
<td>$p = .012^{*}$</td>
<td></td>
</tr>
<tr>
<td>P1 vs P3</td>
<td>$p = .004^{**}$</td>
<td></td>
<td>$p = .015^{*}$</td>
<td></td>
</tr>
<tr>
<td>P2 vs P3</td>
<td>$p &lt;.0001^{**}$</td>
<td></td>
<td></td>
<td>$p = 1$</td>
</tr>
<tr>
<td>Target</td>
<td>$F(15,48)$</td>
<td>$F(15,48)$</td>
<td>$F(15,48)$</td>
<td>$F(15,48)$</td>
</tr>
<tr>
<td></td>
<td>$= 4.08$</td>
<td>$= 6.95$</td>
<td>$= 13.04$</td>
<td>$= 3.27$</td>
</tr>
<tr>
<td></td>
<td>$p &lt;.0001^{**}$</td>
<td>$p &lt;.0001^{**}$</td>
<td>$p &lt;.0001^{**}$</td>
<td>$p = .001^{**}$</td>
</tr>
<tr>
<td>Sessions</td>
<td>$F(30,96)$</td>
<td>$F(30,96)$</td>
<td>$F(30,96)$</td>
<td>$F(30,96)$</td>
</tr>
<tr>
<td>X</td>
<td>$= 1.29$</td>
<td>$= 1.14$</td>
<td>$= 2.71$</td>
<td>$= .54$</td>
</tr>
<tr>
<td>Target</td>
<td>$p = .18$</td>
<td>$p = .31$</td>
<td>$p &lt;.0001^{**}$</td>
<td>$p = .97$</td>
</tr>
</tbody>
</table>

*p<.05; **p<.01

Interestingly, we noticed that the magnitude of the errors was smaller for all the targets located on the left to the grid’s midline (contralateral) than for all of those located to the right of the midline (ipsilateral) for all subjects for the pre- and post-perturbation proprioceptive mapping sessions. Figure
5.8 shows the experimental subjects’ mean error magnitude as a function of target location on the grid.

![Mean Error Magnitude Across the Workspace](image)

Figure 5.8. Mean error magnitude across the workspace as a function of target location, which were arranged in ascending order.

**Mean direction of the estimation errors.** In order to quantify the effect of PA on the direction of the errors, we first used circular statistics on the pooled data across targets and subjects for each PM session. However, we looked at the change in mean direction instead, since the direction of the errors was not uniform across targets within each map or across subjects.

Figure 5.9 displays the mean resultant vector at each target location for the three proprioceptive mapping sessions for two exemplary prism subjects. Indeed, it can be seen that the direction of the errors was not uniform across the workspace for each subject, and neither was the pattern of the direction of the errors uniform across subjects. The Watson-Williams multisample test revealed a statistically significant decrease in the angle between P2 and P3.
compared to the angle between P1 and P2 (see table 5.7). This result suggests that prism adaptation affected the mean direction of the errors in P3 compared to P2. However, it is important to note that the standard deviation of these angles was quite large, which was expected due to the variability in the maps.

Figure 5.9. Mean resultant vector at each target location for the three proprioceptive mapping sessions for two exemplary prism subjects.

Then, we wondered if this result was meaningful at all since we were averaging the angles across target locations. Figure 5.10 shows the mean vector at each target location averaged across subjects for the three proprioceptive sessions. In this figure, we normalized the direction of the errors by setting all the blue vectors (P1) to be aligned with 0° and then rotated the red (P2) and green (P3) vectors with respect to the blue vector.

This figure shows that at some target locations the angle between P2 and P3 was smaller than the angle between P1 and P2. In other words, the red (P2) and green (P3) vectors are very close to each other while the blue vector was rotated farther away, which is indicated by the dotted ellipses. On the other hand, some target locations show a clear effect of the perturbation. This effect can be seen when the blue (P1) and red (P2) vectors are very close to each
other and rotated away from the green (P3) vector, which is indicated by the solid ellipses. This figure suggests that averaging across target locations might not be adequate and the circular statistics result might not be meaningful.

*Figure 5.10.* Normalized mean resultant vector at each target location averaged across subjects for the three proprioceptive sessions.
Table 5.7

*Mean Direction of the Error: Pooled Data Watson-Williams Test*

<table>
<thead>
<tr>
<th>PRISM</th>
<th>P1P2 vs. P1P3</th>
<th>P1P2 vs. P2P3</th>
<th>P1P3 vs. P2P3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sessions</strong></td>
<td>$F(1,318) = 0.63$</td>
<td>$F(1,318) = 2.39$</td>
<td>$F(1,318) = 5.99$</td>
</tr>
<tr>
<td><strong>Stats</strong></td>
<td>$p = .43$</td>
<td>$p = .12$</td>
<td>$p = .015^*$</td>
</tr>
<tr>
<td><strong>Mean Vector</strong></td>
<td>$27.03^\circ$</td>
<td>$29.99^\circ$</td>
<td>$21.44^\circ$</td>
</tr>
<tr>
<td><strong>Circular Std dev.</strong></td>
<td>$34.61^\circ$</td>
<td>$32.51^\circ$</td>
<td>$30.18^\circ$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CONTROLS</th>
<th>P1P2 vs. P1P3</th>
<th>P1P2 vs. P2P3</th>
<th>P1P3 vs. P2P3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sessions</strong></td>
<td>$F(1,126) = 2.09$</td>
<td>$F(1,126) = 0.7$</td>
<td>$F(1,126) = 4.3$</td>
</tr>
<tr>
<td><strong>Stats</strong></td>
<td>$p = .15$</td>
<td>$p = .40$</td>
<td>$p = .04^*$</td>
</tr>
<tr>
<td><strong>Mean Vector</strong></td>
<td>$27.08^\circ$</td>
<td>$35.14^\circ$</td>
<td>$22.3^\circ$</td>
</tr>
<tr>
<td><strong>Circular Std dev.</strong></td>
<td>$28.58^\circ$</td>
<td>$34.17^\circ$</td>
<td>$35.72^\circ$</td>
</tr>
</tbody>
</table>

*$p<.05$*

Following those results, we wanted to investigate if the effect of the perturbation on the direction of the errors was not uniform across the map. Since the maps are not uniform across targets for a subject and varied from subject to subject, we compared the errors across PM sessions for each target and for each subject separately. To this end, we performed circular statistics to compare the direction of the 4 estimation errors (4 repetitions) at each target location for each subject separately. This resulted in 48 comparisons for each subject (P1 vs. P2, P1 vs. P3, P2 vs. P3 x 16 target locations). In specific, we used the Watson-Williams multisample test, which is the circular
analogue of the one-factor ANOVA test, and then the Benjamini-Hochberg procedure to control the false discovery rate (FDR) due to the multiple comparisons. After correcting for multiple comparisons, the Watson-Williams test revealed that the direction of the errors changed for only two experimental subjects and one control subject. Subject #5, the direction of the errors significantly changed at target 2 from P1 to P3 ($p = .001$) and for subject #3, the direction of error significantly changed at 6 different target locations: at target 4, 7, 9, 10, 15, and 16 from P1 to P3 ($p = .007, .002, .001, .004, .003, .006$), as well as at target 15 from P2 to P3 ($p = .005$). For the control subject #1, the direction of the errors significantly changed at target 15 from P2 to P3 ($p = .001$). These results indicate that the direction of the errors rarely changed across proprioceptive sessions as only 9 out of 672 possible comparisons were significant and 11 out of 14 subjects didn’t have any significant changes at all.

**Variable Error of the estimation errors.** We investigated the amount of noise in the system by analyzing the overall variance in the workspace. To this end, we used a 3 time (proprioceptive maps before and after PA: P1, P2, P3) repeated-measures analysis of variance (RM-ANOVA).

Figure 5.11 and 5.12 show the variable error on the x and y directions as well as the total variable error for the three PM sessions across subjects. For the prism subjects (see Table 5.8), the repeated-measures ANOVA indicated that the variable error significantly increased from P1 to P2 ($p = 0.006$) and from P1 to P3 ($p = 0.002$) in the x-direction only. Similarly, the total variance significantly increased from P1 to P2 ($p = 0.001$) and from P1
to P3 ($p = 0.001$). There were not significant results for the control subjects (see Table 5.9). To further investigate whether the variance was different in the x- or y-axis, we used an independent t-test for each proprioceptive session separately. This analysis revealed a significant difference between the variance in the x- and y-axis in P1 (see table 5.10). Taken together, these results suggest that the mean error was more variable along the x-axis than along the y-axis. Secondly, the results also show that the variable error was quite large. Large variance makes it difficult to see any consistent patterns or trends in the data. While the magnitude of the aftereffects was about 5 cm, the variance across the workspace along the x-axis after PA was 28.47 cm$^2$, which corresponds to a deviation of about 5 cm.

![Prism Subjects](image)

*Figure 5.11.* Variable error on the x and y directions as well as the total variable error for the three proprioceptive sessions for the prism subjects
Figure 5.12. Variable error on the x and y directions as well as the total variable error for the three proprioceptive sessions for the control subjects.

Table 5.8

Variable Error X, Y and Total: Repeated-Measures ANOVA Results

Comparing Proprioceptive Sessions Across Prism Subjects.

<table>
<thead>
<tr>
<th>Source</th>
<th>X</th>
<th>Y</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sessions</td>
<td>$F(2,30) = 10.56$</td>
<td>$F(2,30) = 1.33$</td>
<td>$F(2,30) = 13.77$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; .0003^{**}$</td>
<td>$p = .279$</td>
<td>$p &lt; .0001^{**}$</td>
</tr>
<tr>
<td>P1</td>
<td>19.09+/−1.84</td>
<td>28.56+/−3.01</td>
<td>47.69+/−4.34</td>
</tr>
<tr>
<td>P2</td>
<td>25.55+/−2.78</td>
<td>29.73+/−3.45</td>
<td>55.29+/−4.9</td>
</tr>
<tr>
<td>P3</td>
<td>28.47+/−2.54</td>
<td>30.99+/−3.62</td>
<td>59.45+/−4.9</td>
</tr>
<tr>
<td>P1 vs P2</td>
<td>$p = .006^{**}$</td>
<td></td>
<td>$p = .001^{**}$</td>
</tr>
<tr>
<td>P1 vs P3</td>
<td>$p = .002^{**}$</td>
<td></td>
<td>$p = .001^{**}$</td>
</tr>
<tr>
<td>P2 vs P3</td>
<td>$p = .641$</td>
<td></td>
<td>$p = .304$</td>
</tr>
</tbody>
</table>

† Greenhouse-Geisser corrected, *$p < .05$, **$p < .01$
Table 5.9

Variable Error X, Y and Total: Repeated-Measures ANOVA Results

Comparing Proprioceptive Sessions Across Control Subjects.

<table>
<thead>
<tr>
<th>Source</th>
<th>X</th>
<th>Y</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sessions</td>
<td>$F(1.34,20.12) = 5.16$</td>
<td>$F(1.40,20.95) = 1.55$</td>
<td>$F(2,30) = 4.46$</td>
</tr>
<tr>
<td></td>
<td>$p = .012^{*}$</td>
<td>$p = .23^{†}$</td>
<td>$p = .02^{*}$</td>
</tr>
<tr>
<td>P1</td>
<td>13.46+/-1.54</td>
<td>13.77+/-1.70</td>
<td>27.23+/-2.67</td>
</tr>
<tr>
<td>P2</td>
<td>19.01+/-2.79</td>
<td>16.47+/-1.82</td>
<td>35.48+/-3.69</td>
</tr>
<tr>
<td>P3</td>
<td>22.75+/-4.14</td>
<td>14.30+/-1.61</td>
<td>37.04+/-4.92</td>
</tr>
</tbody>
</table>

$^{†}$ Greenhouse-Geisser corrected, $^{*}p < .05$, $^{**}p < .01$

Table 5.10

Independent T-Test Comparing the Variable Error on the X Direction and the Variable Error on the Y Direction.

<table>
<thead>
<tr>
<th>t-test X vs. Y</th>
<th>Prism</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>t(30)= -2.69, $p = .011^{*}$</td>
<td>t(30)= -1.14, $p = .89$</td>
</tr>
<tr>
<td>P2</td>
<td>t(30)= -0.94, $p = .35$</td>
<td>t(30)= -0.76, $p = .45$</td>
</tr>
<tr>
<td>P3</td>
<td>t(30)= -0.57, $p = .57$</td>
<td>t(19.44)= 1.9, $p = .067^{††}$</td>
</tr>
</tbody>
</table>

$^{††}$ Levene’s Test for Equality of Variances: Equal variances not assumed

Changes in proprioceptive estimates as a function of changes in adaptation aftereffects. Since different subjects had different levels of adaptation, we wondered whether the observed change in the magnitude of the errors depended on the level of adaptation to the perturbation. Figure 5.13 shows the changes in the magnitude of the error vector as a function of the changes in aftereffects as a percentage of the
perturbation (20 cm) for each subject. Here, we see that the sensory and motor changes are not correlated ($p = .69$). Additionally, we wondered if this was also true for the visuomotor adaptation. Figure 5.14 shows the changes in the magnitude of the error vector as a function of the changes in aftereffects as a percentage of the perturbation (5 cm) for each subject. The figure shows that the proprioceptive change was not correlated to the amount by which subjects adapted to the perturbation ($p = .85$).

![Prism Subjects](image)

Figure 5.13. Proprioceptive change as a function of adaptation aftereffects for all the prism subjects. Red line represents the linear regression line fitted to all subject’s data.
**DISCUSSION**

The goal of the present study was to induce a bigger recalibration to proprioception than that induced by the visuomotor adaptation so we could test our hypothesis that there would be areas on the workspace more robust to the perturbation than others. To this end, we used a prism adaptation (PA) paradigm to induce a globalized perturbation to the perception of limb position. Then, we measured the estimation errors before and after prism adaptation at 16 target locations across a 2-D horizontal workspace. We analyzed the effect of the PA on the direction and magnitude of the errors at a single-subject level as well as on the pooled data across subjects. Our findings suggest that PA had a significant effect on the magnitude and direction of estimation errors. The single-subject or single-target analysis did not
not reveal a systematic change of neither of these metrics after PA. These results are in agreement with what we reported in Chapter Four, which would suggest that proprioceptive recalibration is independent of the perturbation induced.

The reason behind using prism adaptation was to induce a stronger adaptation to the perturbation than that observed with visuomotor adaptation. It follows that a stronger adaptation should result in larger effects of the perturbation on the proprioceptive map. One advantage of prism adaptation is that the locus of adaptation can be easily manipulated. That is, the magnitude of changes in proprioception and vision due to the misalignment of their corresponding reference frames can be manipulated (Redding et al., 2005). To this end, we manipulated the adaptation locus in order to induce a stronger adaptive shift in the sense of the limb position (proprioception) than in the position sense of the eyes (vision). The locus of this change is dependent on the amount and duration of visual feedback during exposure (Redding & Wallace, 1994). Small movement duration and early visual feedback of the pointing hand has been linked to a stronger change in proprioception (Redding & Wallace, 1994). Here, our results showed that our manipulation of the visual feedback resulted in larger and significant aftereffects in the proprioceptive test (4.42 cm, \(p < .0001\)) than in the visual test (.95 cm, \(p = .89\)). The small and not statistically significant change observed in the VT was as expected based on the manipulation of the visual feedback. These results allowed us to be confident that we had affected proprioception during the prism exposure.
Indeed, we were able to show a stronger adaptation to the perturbation than that observed during visuomotor adaptation. Here, subjects adapted their reaches an average of 5 cm to the right of the target after prism adaptation (20 cm shift), while subjects adapted their reaches an average of 2.5 cm to the right of the target after visuomotor adaptation (5 cm shift). Therefore we were able to double the magnitude of the subjects’ adaptation to the perturbation. This stronger adaptation resulted in almost double the effects on the proprioceptive map. The $x$-component of the magnitude of the errors increased by an average of 1.14 cm after prism adaptation compared to an average of .67 cm after visuomotor adaptation.

The results suggest that the magnitude of the adaptation and proprioceptive change depend on the magnitude of the perturbation.

Although, we have used two different types of perturbations, these results are in agreement with different studies using prism and visuomotor adaptation to test the effect of increasing the magnitude of the perturbation. In a visuomotor study by Salomonczyk et al. (2011), different magnitudes of visuomotor rotations were used ($30^\circ$, $50^\circ$, $70^\circ$) to test its effects on the magnitude of adaptation of subjects’ reaches and on the magnitude of proprioceptive estimations of hand location (Salomonczyk et al., 2011). They found that both changes in adaptation and proprioceptive bias were positively correlated with the magnitude of the distortion. Similarly, a prism adaptation study by Fernandez-Ruiz (1999) in which different groups of subjects wore 10, 20, or 30-diopter prism glasses revealed that the higher the displacement
induced by the prisms, the higher the aftereffects (Fernandez-Ruiz & Díaz, 1999).

Although the magnitude of the adaptation and the magnitude of the perturbation effect on the proprioceptive map were larger for the prism subjects compared to the visuomotor subjects, the percentage of adaptation and change were larger for the visuomotor subjects. The induced shift in pointing/reaching was about 20 cm after prism adaptation and 5 cm after visuomotor adaptation. Subjects adapted 25 % (5 cm) and 50 % (2.5 cm) of the prism and visuomotor adaptation, respectively. Then, the effect of the perturbation on the proprioceptive map was about 20 % (1 cm) of the observed prism adaptation compared to 30 % (0.74 cm) of the observed visuomotor adaptation. These magnitudes are in agreement with what studies have reported for both prism and visuomotor studies. For example, prism adaptation studies report an average of 20-40% adaptation (Fortis et al., 2011; Harris, 1963; Redding & Wallace, 1994; 1996; 2000; Welch et al., 1974), while visuomotor studies report an average of 60-90% adaptation (Cressman & Henriques, 2009; Krakauer et al., 2000; Vetter, Goodbody, & Wolpert, 1999). Therefore, our observed adaptation magnitudes are within the values reported in the literature.

Even though we were able to induce a larger adaptation and larger effects on the proprioceptive map, we were still unable to answer our question of whether there were areas on the workspace that would be more resistant to the perturbation than others. Even with double the magnitude of the adaptation after prism exposure, we still could not overcome the challenges
we encountered during the visuomotor adaptation study. Here, we also observed that the direction and magnitude of the errors varied more across target locations within a map than across maps for a target location, which made it difficult to observe effects at the single-target level. In addition, the magnitude of the adaptation (5 cm) did not surpass the variable error along the x-direction at P3 (28.47 cm^2 ~= 5 cm deviation). Therefore, the results of the prism adaptation also imply that the effect of the perturbation might have been buried in the noise. The variable error along the x-direction at P1 seemed very similar for the prism and visuomotor subjects (~20 cm^2), which suggest that the maps are intrinsically variable. In addition, the variable error along the x-direction increased from P1 to P2 and from P2 to P3 for both perturbations studies. We argue that the increase in variability could be due to the sensory uncertainty in estimating hand location in our estimation task, which could have been amplified by the increase in motor noise due to the active arm movements during the perturbation tests. Both prism and visuomotor subjects complained about arm tiredness after the perturbations tests that came before the proprioceptive mapping sessions. Prism subjects performed pointing movements for 5 minutes during prism exposure right before P3 mapping, which corresponded to an average of 140 pointing movements. Similarly, visuomotor subjects performed 115 reaching movements by dragging their finger on the surface of the table. These observations are in agreement with reports that spindle sensitivity varies with kinesthetic demands and is sensitive to motor noise (Scheidt et al., 2010; Slifkin & Newell, 2000), because spindle afferent signals are mediated by
alpha-gamma coactivation during active movement (Ribot-Ciscar et al., 2000). Therefore, it is possible that subjects’ active movements before P2 and P3 increased the motor noise, which in turn increased the proprioceptive uncertainty and thus increased the variable error.

Interestingly, we observed similar effects of the perturbation on the proprioceptive map after visuomotor and prism adaptation. Both methods induced an increase of the magnitude of the errors along the x-component of the error vector, which is in agreement with the direction of the perturbation. In addition, the mean direction of the error across P3 ( proprioceptive map after perturbation) was closer to the mean direction of the error across P2 than when comparing the mean direction of the error between the baseline maps. Perhaps it’s not surprising that both methods resulted in the same effects since both experimental methods induced a conflict between the visual estimate and the felt position of the hand while subjects reached to a target with misaligned visual feedback of the hand. In order to solve the sensory conflict, subjects adjusted the arm movement in order for the visual representation of the hand to achieve the desired endpoint (Baraduc & Wolpert, 2002; Ghahramani et al., 1996; Krakauer et al., 2000; Redding & Wallace, 1996; Simani et al., 2007; Vetter et al., 1999; Wang, 2005). This visuomotor adaptation results in the formation of a new visuomotor mapping.

On the other hand, studies have shown that the adaptive processes involved during visuomotor adaptation are dependent on visual feedback of the arm (i.e. actual vs. computer generated; early vs. terminal) and on how the distortion is introduced (i.e. gradual vs. abrupt) (Bock, 2005; Bock &
Girgenrath, 2006; Clower & Boussaoud, 2000; Norris et al., 2001; Redding et al., 2005; Redding & Wallace, 1994; Saijo & Gomi, 2010). These results suggest that visuomotor adaptation can be modulated by motor learning conditions. It is evident that the motor learning conditions between our two perturbation studies differed in some ways. The visuomotor study provided visual feedback of the hand in the form of a cursor on an upright computer screen and the perturbation was constrained to a single location on the workspace. In addition, subjects made pointing movements in space during prism adaptation while subjects made reaching movements constrained to the surface of the horizontal table. Finally, tactile feedback during the adaptation and proprioceptive sessions was different for the visuomotor and prism studies. Subjects received tactile stimuli while tracing their fingers on the table during the visuomotor tasks and their fingers were allowed to touch the surface of the grid during the proprioceptive sessions. On the contrary, prism subjects did not receive tactile stimuli during either the prism tasks or proprioceptive sessions.

The fact that these two very different experimental methods induced a similar change to the estimation errors indicates that proprioception is recalibrated to a similar extent regardless of how the perturbation is introduced. These findings suggest that sensory and motor changes may be two independent processes arising from the perturbation, which agrees with recent results by Henriques and colleagues. Her group has shown that changes to estimation of hand location were not affected by different experimental manipulations and did not reveal a correlation between the
magnitude of proprioceptive recalibration and the level of motor adaptation attained (Cressman & Henriques, 2009; 2010; Salomonczyk et al., 2011). They have suggested that sensory and motor changes occur simultaneously but independently of each other. In agreement with this statement, our results also found no significant correlations between the percentage of proprioceptive change and the percentage of adaptation change for either study, which suggest that prism adaptation and visuomotor adaptation might induce similar sensory alignments such that proprioception is remapped to match the visual representation of the hand.

If indeed the two processes are independent, it follows that proprioceptive recalibration might not necessarily be related to localized learning and limited generalization like in the case of motor learning. Our results suggest that proprioception uses a structured (global) internal representation instead of a localized one (set of local solutions). Evidence for this is two-fold. First, the idiosyncrasy in the pattern of errors shapes the entire spatial structure and not just the larger errors at the periphery, which one might expect in the case of a set of local solutions. Second, our local visuomotor adaptation induced a global change on our measure of proprioception, which was similar to the change observed with the global perturbation (prism adaptation). If proprioception used a set of local solutions, then the effect of localized perturbation on our proprioceptive map would have been different from the one observed with the visuomotor adaptation. Unfortunately we were unable to measure the effect of the perturbation at each target location, which would have allowed us to test the
generalization properties of proprioception. It remains to be seen if sensory changes to visuomotor adaptation generalize to different areas of the workspace.

One study has looked at the selective enhancement of proprioceptive acuity following motor learning (Wilson et al., 2010). Their study showed that proprioceptive acuity only improved at the trained location but did not improve at untrained areas of the workspace, which could suggest that the internal representation of arm location is composed of a set of local maps. However, we believe that their result does not contradict our observations. The main difference with their study was that their motor learning manipulation did not induce a misalignment of the sensory systems and thus did not result in a remapping of proprioception. In their task, subjects used a robot to move their hands to visual targets and thus their movements improved over the course of 400 reaches. Then, the researchers measured whether proprioceptive acuity had also improved at the trained location as well as at an untrained location. In contrast to this study, visuomotor adaptation studies and force-field learning that have affected the sense of limb position did not affect proprioceptive acuity (Cressman & Henriques, 2009; Ostry et al., 2010). It is possible that the effect of motor learning on proprioceptive acuity does not involve the same processes as those involved during visuomotor adaptation, which is known to affect the spatial map of proprioception.

Finally, we have to address the fact that control subjects also showed some significant effects. We argue that the effects were barely significant (p >
.4). In the instances when the $p$ value was smaller than .01, we argue that it was still not as small as that of the $p$-value from the analysis on the prism subjects’ data. Therefore, the reason for this small significance result could be due to random variation across subjects and random selection of subjects since our sample size of control subjects was small.
Chapter 6

SUMMARY AND CONCLUSIONS

The work presented in this thesis explored the internal representation of arm location. Specifically, we investigated the structure and calibration of this representation through the analysis of the spatial pattern of hand location estimation errors. To this end, we designed experiments that explored the effect of tactile feedback and hand used on the pattern of errors. We also designed experiments to perturb the structure of the map aimed at exploring the basis of its calibration and nonuniformity. Taken together, the results support the idea that we rely on an underlying systematic and stable representation of limb position in order to estimate arm posture and make movements. A summary of what was accomplished in this thesis and its contribution to the study of proprioception and internal representations is presented below.

Chapter Two examined the spatial pattern of estimation errors across hands, tactile conditions, and subjects. We demonstrated that each subject had a systematic pattern of errors that was remarkably stable across conditions. Yet this systematically stable pattern was different across subjects and not uniform across the workspace. The only change observed was a decrease in the magnitude of the errors when subjects touched the surface of the workspace with their right hand. These findings report new evidence of an internal representation of limb position, one that is systematically stable and idiosyncratic.
The fact that these patterns were systematic and stable indicates the existence of an internal representation of limb position. A characteristic of internal representations (computational maps) is that neurons in this map are tuned slightly different, which results in systematic variations in the coded parameter (limb position) across the workspace. In addition, these maps are believed to perform preset computations based on their intrinsic patterns of connectivity, which would suggest they rely on a stored representation. These intrinsic patterns of connectivity would be constructed through experience and thus would result in an idiosyncratic representation of limb position. In addition, constructing this map through everyday experience would mean that the system is continuously being calibrated, in which some areas would be more calibrated than others.

Chapter Three further explored the role of tactile signals on the pattern of errors by providing electrotactile stimulation when subjects estimated the location of their arms in space. In agreement with the observations in Chapter Two, we demonstrated that the pattern of errors was systematically stable across tactile conditions for each subject. Again, the magnitude of the errors decreased when subjects touched the surface of the grid. These results suggest a specific interaction between the primary somatotopic representation of cutaneous receptors and the internal representation of limb position. Touching the surface of the workspace engaged the primary somatotopic representation of cutaneous receptors in the computations of limb position. Electrotactile stimulation of the fingertip might have not provided meaningful and relevant information to aid the
internal representation of limb position in estimating hand location. Our findings suggest that primary somatotopic representation of cutaneous receptors provides relevant information that can enhance the computation of arm posture but it cannot readily change the stable intrinsic patterns of connectivity in the internal representation of arm position. The interaction between touch and proprioception could be different depending on the task such that one modality might be more dominant when manipulating objects than when estimating limb position.

Chapter Four and Chapter Five investigated the stability and calibration of the internal representation of arm position by perturbing the subject’s sense of limb position. We used two different perturbation paradigms: 1) a virtual reality visuomotor adaptation to induce a local perturbation, 2) and a standard prism adaptation paradigm to induce a global perturbation. Our findings revealed that both perturbations had a similar significant effect on the magnitude and direction of estimation errors across subjects. We also showed no significant correlations between the magnitude of adaptation to the perturbation and magnitude change of the estimation errors. Taken together, these results suggest that the change in proprioception might be independent from the way the system is perturbed. These findings parallel previous results showing no significant correlations between the magnitude of proprioceptive recalibration and the level of motor adaptation attained when using different experimental manipulations. Since the local perturbation induced similar effects on the pattern of errors as those observed after the global perturbation, we propose that the internal
representation of arm location might be constructed with a global solution instead of being composed of a set of local maps.

The studies in this thesis provide new insights into the internal representation of arm location, of which relatively little is known.

**SPECIFIC CONTRIBUTIONS**

**Relationship between touch and proprioception.** Our results revealed a complex relationship between tactile feedback and proprioception, one that provided new insights and yielded new questions.

Several studies on body representations and our sense of embodiment suggest that we have a stable internal representation that encodes the position of our body parts in space and that somatotopic maps interact with such body representations (Berlucchi & Aglioti, 2010; Carruthers, 2008; Longo & Haggard, 2010b; Serino & Haggard, 2010). In agreement with that statement, our results suggest a complex interaction between the two maps.

Our results revealed that physically touching the surface of the workspace had an effect on the magnitude of the errors while artificially activating the cutaneous afferents did not impact the subjects’ estimations of hand location. It follows that the information provided through cutaneous channels need to be meaningful and relevant in order to have an effect. Indeed, a recent study showed that providing information about finger position and object compliance solely through tactile channels was not enough to allow object discrimination above chance levels (Horch et al., 2011).

The first question that arises concerns the information provided by touching the surface of the workspace. What was relevant or meaningful
about contact with the surface that could not be provided by electrotactile stimulation? Although a few studies have reported that tactile feedback helps proprioceptive signals in enhancing end-point accuracy and reducing postural sway (Dickstein, 2005; Helms Tillery et al., 1994; Jeka & Lackner, 1995; Kouzaki & Masani, 2008; Lackner et al., 2000; Lackner & Dizio, 1994; Rabin et al., 2008; Rabin & Gordon, 2004; Rao & Gordon, 2001), it is still not clear what type of information is provided. One group has suggested that tactile feedback provides an accurate spatial metric used to recalibrate and update the representation of the body (Lackner & Dizio, 2000). This suggests that the information provided by touching the surface needs to be spatially meaningful. However, there is also a cognitive component that could explain the difference observed in our studies. If subjects are told that the surface they are touching is not stationary when in fact it is, then tactile feedback is much less effective in influencing proprioception (Lackner & Dizio, 2000). Perhaps subjects rely less in the unstable and noisier information provided by the unstable surface. It follows that in our task subjects could have relied less on the information provided by electrotactile stimulation because it was noisier. It could also be possible that the information provided during the electrotactile task was not meaningful to the CNS due to the way the receptors were activated. Touching the surface of the table activated the mechanoreceptors directly while the electrical pulses activated the afferent nerves. In any case, it remains to be investigated what constitutes a spatially meaningful information.
Perhaps the process by which the somatotopic map interacts with the internal representation of arm location depends on the task. Studies that have probed the interaction between proprioception and touch suggest a two-way relationship. Tactile cues have been shown to improve accuracy of pointing movements and estimations of hand location (Helms Tillery et al., 1994; Jeka & Lackner, 1995; Lackner & Dizio, 1994; Rabin & Gordon, 2004; Rao & Gordon, 2001; Rincon-Gonzalez, Buneo, & Helms Tillery, 2011a; Ro et al., 2000), suggesting that tactile signals can enhance proprioception. Conversely, proprioception has been shown to affect aspects of tactile processing in that posture affects the perception of tactile events (Aglioti et al., 1999; Roberts & Humphreys, 2010; J. P. Warren et al., 2011; S. Yamamoto & Kitazawa, 2001). Although finger posture has been shown to affect the perception of electrotactile stimulation (J. P. Warren et al., 2011), this type of tactile feedback did not affect the perception of limb position in our task. This would suggest a two-way flow of information. When the CNS is solving a purely proprioceptive task such as estimating hand location, relevant tactile information is processed by the internal representation of arm location. On the contrary, when the CNS is computing the perception of a tactile event, the somatotopic map processes relevant proprioceptive information. In this case, the tactile event could be elicited through electrotactile stimulation.

A natural question that follows concerns the location in the CNS of such computations. Do these different computations take place in different places or in the same place in which cells are tuned to both cutaneous and
 proprioceptive information? One line of evidence comes from neurophysiology studies that have shown cells in primary somatosensory cortex to be tuned to both contact and posture events (D. A. D. Cohen et al., 1994; Rincon-Gonzalez, Warren, Meller, & Helms Tillery, 2011b; Weber et al., 2011). Other studies have suggested different areas that might be involved with the internal representation of arm location: these areas include the posterior parietal cortex, the extrastriate body area, fusiform body area, and the insula (Berlucchi & Aglioti, 2010). It could certainly be possible that each of these areas is recruited for a specific task. Therefore, much research remains to be done to understand the role of each of these areas on different tasks that involve both touch and proprioception.

**Idiosyncrasy.** One of the main contributions of this work is the idiosyncrasy of the pattern of errors. We are the first group, to our knowledge, to analyze and show that these patterns are in fact idiosyncratic. We are the first then to suggest that the internal representation of arm location is constructed through experience and not just genetically wired. The significance of these results is that by studying individual subjects responses we can learn something about how the brain works.

The first question to arise is what factors influence the pattern of errors. Given more time and subjects, I would have investigated if arm length, arm spam, shoulder width, gender, age, job experience, education, musical skills, motor skills, etc. were correlated with specific features on the pattern of errors. Our first expectation would be that arm configuration would have a predictable effect on the pattern of errors. Indeed, a few groups
have suggested that variations of proprioception across the workspace can be explained based on the geometry of the arm (Fuentes & Bastian, 2010; van Beers et al., 1998; Wilson et al., 2010). However, we argue that these changes in joint geometry are not enough to predict the pattern of estimation errors. If this were the case, then the patterns would not be as different between subjects as we observed. We propose then that experience (job, sports, musical, etc) could also contribute to the systematic pattern of errors. In fact, one study investigated the influence of some of these factors on the systematic deviations in a bimanual parallelity task (Kappers, 2003). Surprisingly, she reported that gender, job experience, and education were the only factors to influence what subjects haptically perceived as parallel. Similarly, another study showed that dancers as compared to non-dancers were not only better at integrating proprioception but also relied more on proprioception when both proprioceptive and visual information were available (Jola et al., 2011).

In Chapter Four we based our hypothesis partly on the idiosyncrasy of the system. We hypothesized that adaptation to the perturbation would be subject-specific. Our results suggest that this was the case. Each subject’s pattern of errors was affected differently. Even though only a few target locations were affected per subject, these were not the same across subjects. This probably contributed to the fact that we could not find a systematic change to the perturbation. As discussed in Chapter Four, we could have tailored the perturbation to each subject’s map by analyzing the pattern of errors performed during the first session a few days before the experimental
session. This would have allowed us to test more specific hypotheses. Given more time and access to more subjects, I would have induced a local perturbation to different points in the workspace based on each individual’s map. For example, I would have carried out two experiments to induce a perturbation to the point of minimum error and to a point of maximal error to test whether any of these points was more robust to the perturbation than the other. This would have been a more controlled way to perform the experiment, which would have allowed us to more easily compare across subjects. I would expect to find different effects on the pattern of errors between perturbations but the effect of each perturbation would be consistent across subjects.

It is certainly surprising the number of studies that have reported subject-specific patterns of hand estimation errors but only perform group analyses (L. E. Brown, 2003; L. E. Brown et al., 2003; Desmurget et al., 2000; Helms Tillery et al., 1994; Smeets et al., 2006; van Beers et al., 1996; 1998; Vindras et al., 1998; Wann & Ibrahim, 1992). Naturally, group analyses are necessary to find commonalities across subjects. However, single-subject analysis could be as important when the system being measured is constructed through experience. For example, it is widely accepted that subjects rely on auditory feedback during accurate speech. However, one study recently showed that auditory feedback might not be the dominant source for monitoring speech for all subjects (Lametti, Nasir, & Ostry, 2012). In this study of sensory preferences in speech production, some subjects
relied more heavily on proprioceptive feedback, indicating that this process
could also be subject-specific.

Therefore, studies in this and similar fields should take a closer look
to individual behavior before making inferences based on group analyses.
Most importantly, understanding the internal representation of arm location
on an individual basis will be crucial for providing somatosensory feedback to
the user of a prosthetic device.

**Stability.** The other major contribution of this work is the finding
that the pattern of errors was remarkably stable across conditions, hands,
time, and even perturbations. We are the first to compare the spatial pattern
of errors across conditions and thus to show that these patterns are stable.
These results suggest that the internal representation or map involved in
this task relied on a stored representation of limb position and not on a series
of single perceptual snapshots. These results revealed a connection between
our task and an internal representation of arm position.

Perhaps this finding is surprising due to the extent of literature on
somatosensory cortical plasticity. Plastic changes have been shown to occur
by modifications in behavior, through training, alterations in the
environment, and due to injury or disease. In fact, research on topographic
maps such as the somatosensory, visual and auditory, have shown that these
maps are not static and undergo plastic changes (Buonomano & Merzenich,
1998). This capacity for reorganization accounts for certain forms of
perceptual and motor learning. Relevant to our study, multiple groups have
shown perceptual changes to the sensed position of the limb (Cressman &
Henriques, 2009; Haith et al., 2008; Ostry et al., 2010; Wong et al., 2011) as well as changes in the perception of speech sounds following motor learning (Nasir & Ostry, 2009; Shiller, Sato, Gracco, & Baum, 2009). Additionally, functional imaging studies have reported changes in activation in sensory areas following motor (Vahdat, Darainy, Milner, & Ostry, 2011) and perceptual learning (Pleger, 2003).

One question that arises is whether those observed changes in plasticity are long lasting. One of the studies mentioned above reported that the change of the sense position of the limb persisted 24 hours later (Ostry et al., 2010). However, the authors did not report if the effect persisted beyond 24 hours. It is possible that most of those studies induce a short-term type of plasticity that does not persist over time. It follows that there might be different levels of learning such that the cortex is more or less plastic depending on the type and/or magnitude of learning or whether the task is behaviorally relevant.

Given more time to continue experiments, I would repeat the prism experiment to measure the change in the pattern of errors at different time points after the experiment. Based on the magnitude of adaptation, magnitude of the change in the errors, and intrinsic noise of the maps reported in this thesis, I would not expect the reported effects to persist over time. In that case, I would repeat the experiment by increasing the time subjects were exposed to the prism distortion, which should result larger and longer lasting aftereffects. It remains to be seen if the magnitude of the changes in the proprioceptive map increases. However, I would not expect
those changes to persist over time. The reason why I believe that the map will not be significantly affected is due to the stability of the map. To further show the stability of these maps, in 2011 we brought back one subject who had participated in the experiment described in Chapter Two, which was completed in 2008. Figure 6.1 shows the superimposed pattern of errors for one hand across tactile conditions. We performed the same analysis described in Chapter Two and found that all comparisons were significantly similar.

*Figure 6.1. Similarity of pattern of errors across time for an exemplary subject. Left-panel: red vectors correspond to the Touch condition and the blue vectors correspond to the No Touch condition. These two patterns of errors were captured in 2008. Middle-panel: the black vectors correspond to the Touch condition captured in 2008 and the blue vectors correspond to the Touch condition captured 3 years later. Right-panel: the black vectors correspond to the No Touch condition captured in 2008 and the red vectors correspond to the Touch condition captured 3 years later.*

Although we have shown that this system is quite stable, recent studies have shown that proprioception can be affected following motor learning. It is important to note, however, that these studies measured
proprioception through a perceptual test and not by mapping estimation errors. As discussed in Chapter Four, this measure requires the subjects to determine if their hand was to the right or left of the reference, which results in a binary measure. Therefore, changes in proprioception are relatively easy to quantify with their measure of proprioceptive change. A recent study used a similar method to ours to measure the subject’s proprioceptive position sense, which they aimed to disrupt with different position-dependent force fields (Kuling, Brenner, & Smeets, 2012). Their measure of proprioceptive position sense allowed them to construct pattern of errors. In their task, subjects moved their unseen hand to match 10 visual targets across a horizontal workspace. They found that the subject-specific spatial pattern of errors was robust under the force fields. This study suggests that this spatial structure of limb position is robust to perturbations. Although we observed a significant effect of the perturbation on the spatial pattern of errors in the studies described here, the small magnitude of the change suggests that the maps are not easy to perturb.

LIMITATIONS

There are many limitations to the work carried out in this thesis. Most of these issues were addressed at the end of each chapter, but the more general issues are briefly discussed below.

The first limitation of these studies is the sample size. I believe that a larger sample size in each of the experiments would have allowed us to be more confident in our results. This was certainly an issue in Chapter Four where there were only five experimental subjects and in Chapter Five where
there were four control subjects. The first issue related to sample size comes from the fact that not all subjects adapted to the perturbation. Therefore, a larger population of subjects would have yielded a larger percentage of subjects who adapted to the perturbation. The second issue relates to inter-subject variability. When we were interested in averaging across subjects, we would have benefited from a larger sample size.

The second limitation in these works is the passive movements during the estimation task. It is possible that extra noise and variability were induced when subjects were passively moved across the workspace by the experimenter. The movement path and velocity were not controlled. It would have been a more robust and well controlled experiment if instead a servo robot had moved the subjects’ arms. Similarly, head and torso movements were not controlled. These can certainly affect estimating the location of the arm in space if these computations are egocentric and thus depend on the position of the head and torso.

The third limitation relates to attention, which was not controlled or manipulated throughout the experiments presented in this thesis. Attention could have certainly played a role in the subject’s ability to estimate hand location or to adapt to a perturbation. Part of the estimation task relied on the memory of where the hand had just been, so if subjects were not paying attention to where their hand was then it becomes a less reliable memory. The estimation task described in Chapters Two and Three took about an hour to complete. Some subjects looked distracted, which made us wonder if their estimates were reliable. To this end, we decreased the number of target
locations used in Chapters Three and Four, which reduced the experimental
time from 1 hour to 15 minutes. Similarly, the problem with the perturbation
studies was that they were performed in the dark. Again, some subjects
looked distracted and bored during the adaptation tests.

Lastly, one of the biggest limitations to the studies described in
Chapters Four and Five concerns the intrinsic variability of the maps. Our
results showed that both the magnitude and direction of the errors varied
across the workspace on each map. In addition to this, the maps varied in a
different manner across subjects. These two issues made it very challenging
to define a baseline. Having such a variable baseline can certainly make the
analysis more difficult. This is why we analyzed the data differently in the
perturbation chapters compared to the first two studies. The analyses used in
Chapters Two and Three were not sensitive enough to pick up the effects of
the perturbation. Those analyses revealed that the maps were stable after
the perturbation. Therefore, we searched for other methods that would be
more sensitive to small variations. To this end we used repeated measures
ANOVA and circular statistics. However, the challenge persisted when the
magnitude of the effect was smaller than the variability in the maps.

FUTURE WORK

There were several new questions and interesting ideas that emerged
from the studies presented in this thesis. From the first study, we came up
with several directions where to take our studies. We chose to pursue the
idea of studying the calibration of the system by perturbing the map.
However, there were other ideas that could have interesting.
The first question to arise concerned the way in which subjects estimated the location of their hands during the estimation task. We wondered whether the task also involved a transformation from a retinotopic frame of reference into a body-centered reference. In other words, was the memory of proprioceptive targets coded relative to gaze? Recent studies have shown that the brain represents the locations of online and remembered proprioceptive and visual-proprioceptive reach targets relative to gaze (Fiehler, Rösler, & Henriques, 2010; Fiehler, Schütz, & Henriques, 2011; Jones & Henriques, 2010). In addition, they showed that judgments of estimates of position of the remembered targets relative to the unseen position of the hand varied significantly relative to gaze (Fiehler et al., 2010). In specific, we wondered if subjects directed their gaze towards where the hand was while their eyes were closed and the hand was at the target location. If so, did subjects maintain this gaze direction throughout the task so when they opened their eyes they were looking towards the direction of where their hand had been. Here, we propose to control gaze direction to test whether the pattern of errors depend on the retinotopic transformation. To this end, we would repeat the experiment by applying two conditions of gaze. A few modifications to the experimental setup would be necessary: head movements would be constrained with a chin rest, the experiment would be performed in the dark such as that the subjects could keep their eyes open but could not see their hands, and eye movements would be tracked. In the first condition, subjects would be asked to maintain gaze on a fixation light straight ahead while their arms are being moved to the target and back.
the second condition, they would be asked to follow their arm movements with their gaze. I would expect estimation errors to be more accurate when subjects are allowed to follow their arm movements with their gaze.

The second question to come from the first study relates to the idea that the pattern of errors observed in this thesis is task dependent. In other words, the same pattern of errors might not be observed if subjects were asked to estimate hand location in a different way or if the initial position varied. Support for these hypotheses came from two studies. In one study, the authors measured the proprioceptive drift that resulted when subjects moved their unseen hand repeatedly to the same target (Smeets et al., 2006). They compared this drift between proprioceptive targets (left hand) and visual targets and showed that the pattern of errors (direction and magnitude of drift) was different. The other study showed that the perception of initial hand location produced biases on estimating hand location (Vindras et al., 1998). To this end, I could vary my experiment slightly. In one case, I could switch the estimation task such as that the target is presented visually and then subjects have to match the location with their hand. In specific, each of the colored targets on the grid would be an LED that would turn on to indicate the location of the target under otherwise absolute dark lighting conditions. Subjects would then indicate the target location with their hand while their eyes are closed. In the other case, I could vary the initial location of where their hands are right before I moved them to a target. The initial position could be right at the midline in front of their bodies.
would expect a slightly different pattern of errors. However, I expect these patterns to be stable and subject specific.

The third question relates to the stability and idiosyncrasy of the internal representation of arm position. Since we concluded that these maps are constructed through experience and stable because they are constantly being calibrated throughout life, we wondered whether teenagers or children would have a less stable pattern of errors. A few studies have looked at the influence of age on proprioceptive accuracy and shown that children (8-10 years) are less accurate than adolescents (16-18 years) or young adults (mean age 21 years) (Crowe, Keessen, Kuus, van Vliet, & Zegeling, 1987; Goble, Lewis, Hurvitz, & Brown, 2005; Hearn, Crowe, & Keessen, 1989). These studies suggest that refinement of proprioception is the result of experience. Therefore, I would like to repeat the estimation task in children and adolescents. I would expect that the pattern of errors would be more variable and less stable than what was reported in this thesis.

Finally, the last question to arise from the first study relates back to the calibration of the system. Instead of perturbing the spatial pattern of errors, we wonder if we could gain insight into its calibration by enhancing proprioceptive acuity through motor learning. A group recently showed increased proprioceptive acuity following motor learning, in which subjects received feedback and were encouraged to improve their reaches to visual targets (Wong et al., 2011). Specifically, we wondered whether errors would be reduced more in areas of the workspace with large errors than in areas of smaller errors. To this end, we would run two separate experiments, which
would consist of training subjects in two different locations in the workspace. For both, subjects would be trained to make accurate movements to a single visual target located on the “testing” location in the workspace. Then, subjects would complete the estimation task across the workspace.

Similarly, there were a few questions that emerged from Chapters Four and Five. The first evident question is whether a stronger perturbation would result in a bigger change of the estimation errors. It remains to be seen whether a larger magnitude of distortion, duration of exposure, or frequency of exposure would have a stronger effect. I would expect that a longer duration of exposure and repeated exposure would have a bigger effect than a larger distortion. To this end, I would aim to induce a stronger adaptation by having subjects undergo prism exposure twice daily over a period of one week and each exposure session would last 10 minutes. This should result in a strong and persistent adaptation to the perturbation. If the pattern of errors is significantly changed, then proprioceptive recalibration depends on the magnitude of the perturbation. On the other hand, if we observe a similar change to the one reported in this thesis, then the internal representation of arm location is stable and robust to perturbations.

If indeed we are able to induce a stronger change to the pattern of errors and thus show that the change in proprioception depends on the magnitude of the perturbation, then we could answer our second question. Since both a local and a global perturbation affected the pattern of errors in a similar way, we suggested that the internal representation of arm location is one global map and not a set of local maps. Therefore, a local perturbation
should generalize to untrained areas of the workspace. To this end, we would repeat the visuomotor adaptation to induce a stronger local perturbation. Then, we would be able to test our original hypothesis, where the effect of the perturbation should generalize to some areas of the workspace.

**SIGNIFICANCE FOR NEUROPROSTHETICS**

Neural prostheses are devices that can potentially restore movement and sensation to people with motor disabilities, spinal cord injury, or missing limbs. Research toward this goal has shown that signals extracted from the brain can be used to control a variety of external systems such as robotic arms, prosthetic limbs, or computer cursors (Ganguly & Carmena, 2009; L. R. Hochberg et al., 2006; Shenoy et al., 2003; D. M. Taylor, Tillery, & Schwartz, 2002; Velliste, Perel, Spalding, Whitford, & Schwartz, 2008). While most of the research in the past decade has focused on the motor component, progress toward advancing the sensory component is still limited (L. E. Miller & Weber, 2011). Even the most sophisticated motor control of a prosthetic device cannot compensate for the lack of somatosensory feedback, which would result on a prosthetic device with limited capabilities. High-quality sensory feedback will enable the user to know where the prosthetic arm is in space and to feel what the prosthetic arm is touching.

The findings presented in this dissertation highlight possible challenges in providing naturalistic sensory feedback to the user of a neural prosthesis.

Our finding that the internal representation of arm location is constructed through experience and thus subject-specific, would suggest that
providing somatosensory feedback to the user of a neuroprosthetic device requires a subject-specific stimulation pattern to the somatosensory cortex or wherever this map may be. Consequently, this would require mapping each patient’s spatial representation of arm location first. This is certainly not trivial or practical. Nonetheless, this individualized process could result in the most accurate way to provide reliable and naturalistic feedback.

The question to arise is whether providing subject-specific stimulation patterns would be more appropriate than allowing plasticity to adapt to a standard stimulation pattern. Studies on learning-related changes in motor areas have shown that plasticity could enhance the performance of prosthetic devices (Jarosiewicz, Chase, Fraser, Velliste, & Kass, 2008; Paz & Vaadia, 2004). However, it reminds to be determined if the plasticity in sensory areas could also enhance the performance of these devices. Our findings suggest that this might not be the case. Here we have shown that the internal map of hand location is stable and robust, which would suggest that plasticity in this area might not be enough to drive adaptation to a standard stimulation pattern. In other words, users might not be able to learn or create a new stable internal representation of hand location.

Finally, our results also suggest that this representation is not capable of local changes but instead changes as a whole. This would imply that in order to provide adequate sensation the whole population of neurons corresponding to the map might need to be stimulated instead of relaying on a subset of neurons.
Nonetheless, the relevance of these proposed challenges remain to be investigated. Further understanding of this internal representation of hand position will be necessary for providing both stable and adaptive sensory feedback in neuroprosthetic applications.
REFERENCES


APPENDIX A

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In addition, sections of Chapter Two have been published in IEEE Transactions on Neural Systems and Rehabilitation Engineering. The IEEE does not require individuals working on a thesis to obtain formal reuse license. Below is the full citation associated with this published work:

Title: Haptic Interaction of Touch and Proprioception: Implications for Neuroprosthetics
Publication: Neural Systems and Rehabilitation Engineering, IEEE Transactions on
Publisher: IEEE
Date: Oct. 2011
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Chapter Three is currently in press in the Journal of Motor Behavior and therefore permission is pending.


In press
PERMISSIONS FROM CO-AUTHORS

Co-authors on previously published or in press articles “The Proprioceptive Map of The Arm Is Systematic And Stable, But Idiosyncratic”, “Haptic Interaction of Touch and Proprioception: Implications for Neuroprosthetics”, and “Interactions between tactile and proprioceptive representations in haptics” have granted their permission for use of the articles in this dissertation.
APPENDIX B

INSTITUTIONAL REVIEW BOARD FORMS
To: Stephen Helms Tillery  
ISTB1 181F

From: Anna Schwartz, Chair 
Institutional Review Board

Date: 09/15/2006

Committee Action: Expedited Approval

Approval Date: 09/15/2006

Review Type: Expedited F4 F7

IRB Protocol #: 0609001085

Study Title: Electrotactile Exploration of 2D Space

Expiration Date: 09/14/2007

The above-referenced protocol was approved following expedited review by the Institutional Review Board.

It is the Principal Investigator’s responsibility to obtain review and continued approval before the expiration date. You may not continue any research activity beyond the expiration date without approval by the Institutional Review Board.

Adverse Reactions: If any untoward incidents or severe reactions should develop as a result of this study, you are required to notify the Institutional Review Board immediately. If necessary a member of the IRB will be assigned to look into the matter. If the problem is serious, approval may be withdrawn pending IRB review.

Amendments: If you wish to change any aspect of this study, such as the procedures, the consent forms, or the investigators, please communicate your requested changes to the Institutional Review Board. The new procedure is not to be initiated until the IRB approval has been given.

Please retain a copy of this letter with your approved protocol.
You are being asked to read the following material to ensure that you are informed of the nature of this research study and how you will participate in it, if you consent to do so. Signing this form will indicate that you have been so informed and that you give your consent. Federal regulations require written informed consent prior to participation in this research study so that you can know the nature and risks of your participation and can decide to participate or not to participate in a free and informed manner.

Introduction
The purposes of this form are to provide you (as a prospective research study participant) information that may affect your decision as to whether or not to participate in this research and to record the consent of those who agree to be involved in the study.

Researchers
Steven Helms Tillery, Assistant Professor in the Harrington Department of Bioengineering and Associated Faculty in the Department of Kinesiology at Arizona State University, along with his research students Jay Warren and Libiana Raxon have invited you to participate in a research study.

Purpose
You are being invited to participate in a study to examine the ability to determine the location of your fingertip on a grid with and without the aid of stimuli applied to the fingertip. The information gained in this experiment will allow us to better understand the body’s ability to determine its location in space as well as identify the possible role of additional sensory information.

Selection Criteria
Any healthy adult (21 yrs of age or older) without previous history of neuromuscular disease or nerve injury to the hand is invited to participate. If you have previous history of neuromuscular disease or nerve injury to the hand, you can not participate in this study. Approximately twenty to thirty subjects will be enrolled in this study to participate in the three experimental conditions outlined below.

Procedures
This experiment uses electrotactile stimulation. This type of stimulation involves the use of electricity to stimulate your nerve endings through the skin. The sensations you will feel will vary from "fast blood pulses" to "vibration" to small electrical feeling pulses. To begin you must wash your hands and then we will further clean your fingertip with isopropyl alcohol. Then we place an electrode on your fingertip with electrode gel and a piece of tape. After the electrode has been properly placed on your fingertip, the electrode will be hooked up to the stimulator and a grounding electrode will be placed around your finger. Stimulation will begin with very small amounts of current and the current levels will be increased until you can feel the stimulus. The level of sensation we are looking for is perceptual threshold. This sensation occurs after you can first feel the stimulus. Once you begin to feel the stimul,
you should feel a sensation similar to blood pulsing in your fingertip. This sensation will intensify as the current is increased. Perceptual threshold is reached when the feeling changes from this vibration/pressure feeling similar to blood into small, distinct, electrical feeling pulses. Once you reach perceptual threshold we will verify that you can feel this stimuli several times and ensure that it is at its lowest possible level. Once a comfortable stimulation level is identified the trial will begin. If at any time during the trial you stop feeling the electrical stimuli let the experimenter know and the trial will be stopped so that the stimuli can be adjusted back to your perceptual threshold.

You will be sitting here in the chair with yourself aligned with the centerline of the grid. Your right hand should be comfortably closed with your right index finger extended in a pointing fashion. During the experiment we will ask you to close your eyes previous to moving your hand over the grid. With your eyes closed we will navigate your hand over a point on the grid and stimulate you for approximately 3 seconds. Then we will return your hand to the resting position. Once your hand is back in the resting position you may open your eyes and as quickly as possible tell me the coordinate where you believe your index finger was pointing. If you are unsure of the location your finger was pointing at give your best guess. The entire experiment from this point on will last between 30 and 45 minutes. You will be re-contacted for the purpose of being recruited for another session of the same length where the same procedure will take place but with no electrical stimulation. You will be asked to come back to the test site a total of three times to carry out the three different experimental conditions.

**Discomforts**

There is no discomfort involved in this experiment.

**Risks**

There is no risk involved in this experiment.

**Benefits**

The study will be of no direct benefit to you. This study will help us better understand how tactile and electrical stimuli affect somatosensory information.

**New Information**

If the researchers find new information during the study that would reasonably change your decision about participating, then they will provide this information to you.

**Confidentiality**

All information obtained in this study is strictly confidential unless disclosure is required by law. The results of this research study may be used in reports, presentations, and publications, but the researchers will not identify you. In order to maintain confidentiality of your records, Steve Helms Tillery along with Jay Warren and Liliana Rincon will be assigned a subject code and my identity will be known only by the principal investigator and those individuals who work in his laboratory. Steve Helms Tillery alone will control access to the results when they are published and afterwards.
Withdrawal Privilege

It is ok for you to say no. Even if you say yes now, you are free to say no later, and withdraw from the study at any time. Your decision will not affect your relationship with Arizona State University or otherwise cause a loss of benefits to which you might otherwise be entitled.

Participation Costs and Subject Compensation

There are no associated costs or payments for your participation in this study.

Compensation for Illness or Injury

If you agree to participate in the study, then your consent does not waive any of your legal rights. However, in the event of (harm, injury, illness) arising from this study neither Arizona State University nor the researchers are able to give you any money, insurance coverage, free medical care, or any compensation for such injury.

Voluntary Consent

Any questions you have concerning the research study or your participation in the study, before or after your consent, will be answered by Jay Warren or Liliana Rincon, ISTB1 181, (480) 727-9193 or Steven Helms Tillery, ISTB1 181 E, (480) 965-0753

If you have questions about your rights as a subject/participant in this research, or if you feel you have been placed at risk, you can contact the Chair of the Human Subjects Institutional Review Board, through the ASU Research Compliance Office, at 480-965 6788.

This form explains the nature, demands, benefits and any risk of the project. By signing this form you agree knowingly to assume any risks involved. Remember, your participation is voluntary. You may choose not to participate or to withdraw your consent and discontinue participation at any time without penalty or loss of benefit. In signing this consent form, you are not waiving any legal claims, rights, or remedies. A copy of this consent form will be given (offered) to you.

Your signature below indicates that you consent to participate in the above study.

<table>
<thead>
<tr>
<th>Subject's Signature</th>
<th>Printed Name</th>
<th>Date</th>
</tr>
</thead>
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INVESTIGATOR’S STATEMENT

“I certify that I have explained to the above individual the nature and purpose, the potential benefits and possible risks associated with participation in this research study, have answered any questions that have been raised, and have witnessed the above signature. These elements of Informed Consent conform to the Assurance given by Arizona State University to the Office for Human Research Protections to protect the rights of human subjects. I have provided (offered) the subject/participant a copy of this signed consent document.”

<table>
<thead>
<tr>
<th>Signature of Investigator</th>
<th>Date</th>
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</table>
PROTOCOL COVERING CHAPTERS FOUR AND FIVE

To: Stephen Helms Tillery
    ISTB1

From: Carol Johnston, Chair
       Biosci IRB

Date: 03/01/2012

Committee Action: Expedited Approval

Approval Date: 03/01/2012

Review Type: Expedited F4

IRB Protocol #: 1202007431

Study Title: Tactile and Proprioceptive Senses in the Upper Limb of Humans

Expiration Date: 02/28/2013

The above-referenced protocol was approved following expedited review by the Institutional Review Board.

It is the Principal Investigator’s responsibility to obtain review and continued approval before the expiration date. You may not continue any research activity beyond the expiration date without approval by the Institutional Review Board.

Adverse Reactions: If any untoward incidents or severe reactions should develop as a result of this study, you are required to notify the Biosci IRB immediately. If necessary a member of the IRB will be assigned to look into the matter. If the problem is serious, approval may be withdrawn pending IRB review.

Amendments: If you wish to change any aspect of this study, such as the procedures, the consent forms, or the investigators, please communicate your requested changes to the Biosci IRB. The new procedure is not to be initiated until the IRB approval has been given.

Please retain a copy of this letter with your approved protocol.
CONSENT FORM
Tactile and proprioceptive senses in the upper limb of humans
SensoriMotor Research Group Laboratory, ISTB1, PEBE, & Bio-B
School of Biological and Health Systems Engineering, Arizona State University

INTRODUCTION
The purposes of this form are to provide you (as a prospective research study participant) information that may affect your decision as to whether or not to participate in this research and to record the consent of those who agree to be involved in the study.

RESEARCHERS
Stephen Helms Tillery, Assistant Professor in the Harrington Department of Bioengineering, Associated Faculty in the Department of Kinesiology, and Associated Faculty in the Department of Psychology at Arizona State University, along with his research students Cynthia Pierce, Justin Tanner, and Liliana Rincon Gonzalez have invited you to participate in a research study.

STUDY PURPOSE
Several studies have been conducted looking into how humans can identify very small differences between objects. Typically, when a person grasps an object, they use either vision, touch, or a combination of vision and touch to gain information about that object. This research study is focused on gaining a better understanding of size discrimination using touch.

DESCRIPTION OF RESEARCH STUDY
If you decide to participate, then you will join a study which examines the role various sensory modalities used for object manipulation and identification (including touch, pressure, and position in space). There are several variations of the experiment which you will be participating in, but all are described by the following:

Most experiments will take place in PEBE 158B, where a system of three motion tracking cameras is set up. You will be seated in the center of the room and a virtual reality environment will be presented in a computer monitor or head mounted display. Motion tracking markers will be attached to your hand and arm via a glove, glue, tape, or Velcro straps. In a similar manner, small tactors or vibrating motors may be placed on your arm also.

If you have been recruited for an electrotactile experiment, you will also have electrodes placed on one or more fingertips. These small electrodes allow us to pass current through your skin that directly stimulates nerve endings. The sensations you experience will vary from "fast blood pulses" to "small electrical feeling pulses". Your fingertips will be prepared by cleaning with swabs and isopropyl alcohol. The electrode will be placed onto your fingertip with electrode gel and a small piece of tape. We will identify your threshold for the stimulation by slowly turning up the current strength until you begin to feel the stimulation. The sensation will intensify as we turn up the current further to identify a good current strength for your experiment. At no point should you experience painful sensations. If you do, or if you stop feeling the sensation during the experiment, please let the experimenter know immediately.

Some experiments will also take place in BioB BL1-93B. There is a motion tracking system of eight cameras set up in the room. A virtual reality environment may be presented in a computer monitor or head mounted display. Motion tracking markers may be attached to your
hand and arm via a glove, glue, tape, or Velcro straps. Additionally, a robotic arm may be used to present objects for you to interact with.

You may be asked to grasp a variety of objects that differ in texture, size, shape, or other characteristic and compare the object to a previously felt object. The objects may remain stationary or move in a controlled manner while you are touching it. Virtual reality may be used in conjunction with or in place of physical objects, and interactions between your hand and virtual reality environment may be signified by vibration.

In other experimental sessions, your arm may be passively moved to a location in space, and you will be asked to estimate the position of your hand in space. You may be asked to reach for targets within a virtual reality environment, and a shift, rotation, or other perturbation may affect the position of their cursor relative to physical space. In some instances, we will introduce a perturbation to your visual experience by having you wear displacing prisms for up to an hour. These prisms move the visual world to the left or right, and lead subjects to remap the relationships between sensory stimulation and movement. This experience has no lasting consequences.

You will be offered and allowed to take breaks throughout the experiments when pauses will not interfere with data collection. You may be asked questions about the strategy you used to achieve task goals and assumptions that you made about the task.

If you say YES, then your participation will last for no longer than 2 hours per experimental session up to 4 experimental sessions in PEBE 158B or BL-93B of Bodesign-B, on Arizona State University’s Tempe Campus Location. Approximately 100 people will be enrolled in this study. Your identity will not be

By signing the following, you hereby certify that you are between 18 and 65 years old and are generally healthy. You have NOT had any history of neurological disease.

RISKS
There are no known risks from taking part in this study, but in any research, there is some possibility that you may be subject to risks that have not yet been identified.
All data collected from this study will be identified only by subject number to protect your identity.

BENEFITS
This study will be of no direct benefit to me. There are possible future benefits to the understanding of the brain and how it interprets afferent signals. These include prosthetics that provide better touch sensations to the user and haptic devices that provide a clearer ‘image’ of the artificial world being ‘displayed’ on these devices.

CONFIDENTIALITY
All information obtained in this study is strictly confidential unless disclosure is required by law. The results of this research study may be used in reports, presentations, and publications, but the researchers will not identify you. In order to maintain confidentiality of your records, Stephen Helms Tillery along with Cynthia Pierce, Justin Tanner, or Liliana Rincon will be assigning a subject code and your identity will be known only by the principal investigator and those individuals who work in this laboratory. Stephen Helms Tillery alone will control access to the results when they are published and afterwards.

SIGNATURE

Date 6-12-2012

ASU IRB
Approved

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WITHDRAWAL PRIVILEGE
Participation in this study is completely voluntary. It is ok for you to say no. Even if you say yes now, you are free to say no later, and withdraw from the study at any time.

COSTS AND PAYMENTS
There is no payment for your participation in the study.

VOLUNTARY CONSENT
Any questions you have concerning the research study or your participation in the study, before or after your consent, will be answered by Cynthia Pierce, Justin Tanner, or Liliana Rincon in person or can be answered by them via email correspondence at cdpierce@asu.edu, jctanner@asu.edu, or liliana.rincon@asu.edu or by appointment in ISTB1 181 at Arizona State University’s Tempe Campus. The principal investigator, Stephen Helms Tillery, can similarly be reached for inquiries via email at stillery@asu.edu, by appointment in his office, located at ISTB1 181F at Arizona State University’s Tempe Campus, or via phone at (480) 965-0753. Written correspondence can be mailed to any of the investigators at the following address:

SMoRG Laboratory
ECG 334 Box 870709
School of Biological and Health Systems Engineering
Arizona State University
Tempe, AZ 85287-9709

If you have questions about your rights as a subject/participant in this research, or if you feel you have been placed at risk; you can contact the Chair of the Human Subjects Institutional Review Board, through the ASU Office of Research Integrity and Assurance, at 480-965 6788.

This form explains the nature, demands, benefits and any risk of the project. By signing this form you agree knowingly to assume any risks involved. Remember, your participation is voluntary. You may choose not to participate or to withdraw your consent and discontinue participation at any time without penalty or loss of benefit. In signing this consent form, you are not waiving any legal claims, rights, or remedies. A copy of this consent form will be given (offered) to you.

Your signature below indicates that you consent to participate in the above study

Subject’s Signature                  Printed Name                  Date

INVESTIGATOR’S STATEMENT
"I certify that I have explained to the above individual the nature and purpose, the potential benefits and possible risks associated with participation in this research study, have answered any questions that have been raised, and have witnessed the above signature. These elements of Informed Consent conform to the Assurance given by Arizona State University to the Office for Human Research Protections to protect the rights of human subjects. I have provided (offered) the subject/participant a copy of this signed consent document.”

Signature of Investigator                  Date
ANIMAL PROTOCOL COVERING THE WORK PRESENTED ON

APPENDIX C

Institutional Animal Care and Use Committee (IACUC)
Office of Research Integrity and Assurance
Arizona State University

Tempe, Arizona 85287-1103
(480) 965-2179   FAX: (480) 965-7772

Animal Protocol Review

ASU Protocol Number: 10-1101R
Protocol Title: Investigations of Central Synaptic Transmission and Plasticity
Principal Investigator: William Tyler
Date of Action: 12/31/2009

The animal protocol review was considered by the Committee and the following decisions were made:

☐ The original protocol was APPROVED as presented.
☒ The revised protocol was APPROVED as presented.
☐ The protocol was APPROVED with RESTRICTIONS or CHANGES as noted below. The project can only be pursued, subject to your acceptance of these restriction or changes. If you are not agreeable, contact the IACUC Chairperson immediately.
☐ The Committee requests CLARIFICATIONS or CHANGES in the protocol as described in the attached memorandum. The protocol will be reconsidered when these issues are clarified and the revised protocol is submitted.
☐ The protocol was approved, subject to the approval of a WAIVER of provisions of NIH policy as noted below. Waivers require written approval from the granting agencies.
☐ The protocol was DISAPPROVED for reasons outlined in the attached memorandum.
☐ The Committee requests you to contact ________________ to discuss this proposal.
☐ A copy of this correspondence has been sent to the Vice President for Research.
☐ Amendment was approved as presented.

RESTRICTIONS, CHANGES OR WAIVER REQUIREMENT:
Approved # of Animals: 2340, 1200, 300 36, 360   Pain Level: B, C, D, B, C
Species: Mice, Rat
Approval Period: 12/31/2009 – 12/30/2013

Signature: ___________________________ Date: _____________
IACUC Chair or Designee

Original: Principal Investigator
cc: IACUC Office
     IACUC Chair
ANIMAL USE PROTOCOL
ARIZONA STATE UNIVERSITY INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE
(revised March 2009)

Please read "Instructions for Completing the Animal Use Protocol" before completing. Upon approval, this protocol will become a public record so please follow instructions carefully.

PROJECT/PROGRAM TITLE: Investigations of Central Synaptic Transmission and Plasticity
SPECIES REQUESTED: Mus musculus, Rattus norvegicus

I. PERSONNEL INFORMATION

A. A single member of the university faculty and/or Principal Investigator (PI) is considered the responsible individual.

NAME: William J. Tyler
TITLE: Assistant Professor

AFFILIATION: SOLS
Cell Phone #: 480-985-6899
Fax # 480-985-6899
Office Phone # 480-727-8605
Dept. Phone #: 480-965-0803
E-Mail: wtyler@asu.edu

B. Additional contact, if any, for IACUC business

NAME: 
TITLE: 

AFFILIATION: 
Cell Phone #: 
Fax #: 
Office Phone #: 
Dept. Phone #: 
E-Mail: 

C. Protocol Type

X Non-funded research
Grant / Contract (Also submit grant proposal with this protocol)

Granting Agency: 
Proposal Title: 
Proposal Number: 
Co-Investigator(s): 

Teaching
Course Title, Schedule: 

Revision 3/13/2009
D. Protocol Status:
- [ ] New
- [x] Renewal—Previous Protocol #: 07-014R
- [ ] Revision—Previous Protocol #:

E. List all persons involved in this protocol. The first person listed should be the PI.

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Role in Protocol (What procedures will each person be doing?)</th>
<th>Species with which individual will have direct contact (&quot;all&quot; or list species)</th>
<th>ACUC USE ONLY (Training Imminently)</th>
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<td>William Tyler</td>
<td>PI</td>
<td>All</td>
<td>All</td>
<td>12/09</td>
</tr>
<tr>
<td>Yusuf Tufail</td>
<td>Graduate Student</td>
<td>All</td>
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<tr>
<td>Monica Li Tauchmann</td>
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<td>All</td>
<td>All</td>
<td>12/08</td>
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<tr>
<td>Anna Yoshinori</td>
<td>Graduate Student</td>
<td>Culture preparation</td>
<td>All</td>
<td>12/09</td>
</tr>
<tr>
<td>Joshua Nichols</td>
<td>Undergraduate Student</td>
<td>behavior</td>
<td>Mice</td>
<td>12/09</td>
</tr>
<tr>
<td>Liliana Rincon</td>
<td>Graduate Student</td>
<td>Culture preparation</td>
<td>All</td>
<td>12/09</td>
</tr>
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* The answer provided in this column dictates which Level II species-specific IACUC training modules are required for each individual. An individual only needs to complete Level II certification for those species with which he or she will directly work.

**Note:** ASU requires that all personnel engaged in animal research or teaching be qualified through training or experience in order to conduct the work humanely. The IACUC requires the successful completion and renewal of Level I – The Humane Care and Use of Laboratory Animals as well as Level II species-specific training at least once every 3 years. A link to the individual training modules is available on the IACUC ASU homepage at: http://hazelforest.net/latineticlient/asu/introduction.htm.

F. Have all personnel on this protocol completed the required IACUC Level I and Species-Specific Level II Training Modules as well as the Occupational Health and Safety Program Health Surveillance Questionnaire? The Training Modules and the Health Surveillance Questionnaire (HSQ) can be found at http://researchintegrity.asu.edu/iacuc/training/exams.htm

- [x] Yes. Proceed to section B.
- [ ] No. List the individuals who are not in compliance and identify their deficiencies with an "X" in the appropriate columns:

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Revision 3/13/2009
APPENDIX C

OPTOGENETICS WORK
The following document was submitted as part of the prospectus examination required to gain candidacy. This document presents the work accomplished in the first two years of the doctorate program as well as for the proposed work to be done in the following years. The aim of that project was to investigate an alternative to intracortical microstimulation to provide sensory feedback to the user of a prosthetic hand. The problem with intracortical microstimulation is its poor long-term reliability, limited cell specificity, and low spatial resolution. To address those issues, we proposed to use light stimulation of genetically modified cortical neurons. Optogenetic tools such as Channelrhodopsin-2 (ChR-2) have the potential of long-term reliability, cell-specificity, and fast kinetics. ChR-2 is a light sensitive protein that induces temporally precise depolarization of the cell membrane when activated with blue light at low intensities. Currently, in vivo studies using ChR-2 rely on invasive light sources that provide little or no capability for patterned activation. These light sources typically rely on traditional LEDs of fiber-optic coupled diode lasers. We propose to use Organic Light Emitting Diodes (OLEDs) as the light source for non-invasive patterned activation of the cortex. OLEDs differ from traditional LEDs in that their emissive electroluminescent layer is composed of a thin organic film placed between two electrodes. These organic compounds allow the design of flexible, easily customizable, and ultra-thin displays that have extremely high fluorescent efficiencies, resolutions and fast switching times.
RESEARCH PROSPECTUS

Liliana Rincon Gonzalez
Research Prospectus
SensoriMotor Research Group
School of Biological and Health Systems Engineering
February 2010
Patterned optical activation of Channelrhodopsin-2 neurons using organic LEDs

A. Specific Aims

Interfaces between neural tissue and external devices capable of providing sensorimotor feedback are highly desired for use in smart prosthetics. Currently, sensorimotor feedback in neuroprosthetics is commonly achieved using electrical stimulation of the peripheral and central nervous system. However, direct stimulation of the brain could provide a more direct and natural control of prosthetics. For example, this technology could improve the control of a prosthetic by providing information about touch, temperature, limb position, and/or grip force. The current electrical stimulation methods have numerous shortcomings including poor reliability in chronic settings, limited cell specificity, and low spatial resolution. Of these the largest problem is poor reliability in chronic settings, brought on by a foreign body reaction to the implant. This reaction is elicited by the activation of reactive astrocytes and microglia resulting in encapsulation of the device and increasing tissue impedance. As a result, more current is needed to achieve the same activation levels. This can lead to electrode damage, overheating of the tissue, and tissue damage. An additional problem inherent in electrical stimulation involves the indiscriminate activation of multiple neuron types over a large radius due to the electric field produced around the electrode.

Photostimulation, rather than electrical stimulation of a neuron can overcome many of these limitations. Emerging optogenetic tools such as channelrhodopsin-2 (ChR-2) have the potential of long-term reliability, cell-specificity, and fast kinetics. ChR-2 has already been used to activate neuronal circuits in a multitude of preparations. ChR-2 is a non-selective cation channel, native to algae, that induces depolarization of the membrane when activated with ~480nm light at intensities as low as 1mW/mm²/2. This protein can be readily expressed in mammalian neurons using viruses, transfection, and transgenic methods.

There are a few methods for introducing photons into neural systems for use in light-mediated stimulation. These methods typically rely on traditional LEDs or fiber-optic coupled diode lasers. Organic Light Emitting Diodes (OLEDs), provide a few benefits which make them a better choice for light-mediated stimulation of neural tissue. These OLEDs differ from traditional LEDs in that their emissive electroluminescent layer is composed of a thin film of organic polymers or small organic molecules. These organic compounds allow the design of easily customizable, flexible, and ultra-thin displays with extremely high resolutions and switching times. These are desired features for designing neuroprosthetics requiring high spatiotemporal specificity for accurate and robust sensorimotor feedback.

In this proposal, we propose to test the concept that an OLED can not only activate a ChR-2 cell, but can also discretely activate several ChR-2 neurons. **Our overall aim is to stimulate ChR-2 expressing neurons in a pattern of activity using an OLED display.** To determine the OLED parameters that effectively activate ChR-2 neurons, I propose a series of electrophysiological experiments that will characterize the response properties of ChR-2 neurons to different OLEDs settings. To determine what basic light mediated OLED characteristics (size, current needs, light intensity, peak emission wavelength, light pulse duration, and frequency of light pulses) best induce photocurrents (via channel activation), I propose performing experiments using a monolayer of cells (dissociated cultures). The monolayer of cells in primary cultures will limit the light scattering, allowing me to easily characterize these different properties of OLEDs when used to activate ChR-2 neurons. To determine the effects of cortical tissue thickness on the ability of the light to activate the light-sensitive channels in a volume of tissue, I propose performing experiments using acute brain slices to measure how much the photocurrents decrease with increasing thickness.

**Specific Aim 1: Prototype an OLED display to drive a group of ChR-2 cells in a pattern of activity.** With the knowledge gained from the proof-of-concept experiments, I will design an OLED display to elicit patterned activation of ChR-2 neurons. Using dissociated cultures and optical imaging methods, I will arrange OLEDs for discrete and sequential activation of ChR-2 cells. Using the
monolayer of cells, I will refine the specifications of the OLEDs to activate distinct cells achieving both high temporal and spatial resolutions. Then, I will validate these stimulation specificity results by using the OLED array on acute brain slices while recording the evoked activity using optical imaging methods.

**Significance**

The proposed work provides an alternative to electrical stimulation of neural tissue with potential applications in treatment of patients with spinal cord injury and with amputations, as well as a variety of patients with sensorimotor dysfunctions. In addition, this work has major applications to our future efforts. It provides a way to elicit patterned activation of ChR-2 neurons, which would enable us to test sensory neuroprosthetic devices in trained non-human primates. Although this is not a direct goal of this work, it will fit in the broad context of the Sensorimotor Research Group Lab, which focuses on studies sensorimotor learning and representations in the nervous system to design neuroprosthetic devices.

**B. Background**

Research on neuroprosthetics has experienced an impressive growth in the past decade since the first demonstrations of real-time control of a device by recorded motor cortex neurons (Chapin, Moxon et al. 1999). Developments in this field have ranged from real-time control of 3-D movements (Wessberg, Stambaugh et al. 2000; Serruya, Hatsopoulos et al. 2002; Taylor, Tillery et al. 2002; Taylor, Tillery et al. 2003) to functional examination of cortical areas capable of driving the devices (Hatsopoulos 2005; Hatsopoulos, Xu et al. 2007; Wu and Hatsopoulos 2007). In addition, much effort has been focused on identifying computational methods for the extraction of neural signals needed to control the neuroprosthetic devices (Schwartz, Taylor et al. 2001; Serruya, Hatsopoulos et al. 2003; Shenoy, Meeker et al. 2003; Brockett, Rojas et al. 2004; Brown, Kass et al. 2004; Eden, Truccolo et al. 2004; Kemere, Shenoy et al. 2004; Srivastava and Brown 2007; Srivastava, Eden et al. 2007). These efforts have culminated in human subjects implanted with microelectrode arrays through which they could directly control the motion of a cursor on a computer screen (Donoghue, Nurmikkko et al. 2004; Friehs, Zerris et al. 2004).

In order to move from controlling a computer cursor to having a robotic arm control the cursor like a real hand would, continuous peripheral tactile and proprioceptive feedback needs to be relayed back to the neuroprosthetic device. Current neuroprosthetic designs rely on visual feedback (Serruya, Hatsopoulos et al. 2002; Taylor, Tillery et al. 2002; Carmen, Lebedev et al. 2003; Lebedev, Carmen et al. 2005), which makes control of the prosthetic outside the field of vision very difficult. To better control these devices it is important to develop a system for somatosensory feedback that is capable of relaying physiologically relevant information, including proprioception and tactile reception. Much research exists that can be used to support this goal including studies of tactile receptive fields, arm posture, reach, and grasp in primate primary somatosensory cortex (S1) (Cohen, Smaulbone et al. 1994, Tillery, Soechting et al. 1996, Gardner, Ro et al. 1999, Gardner, Ro et al. 2007). Furthermore, primates trained to discriminate between different mechanical stimuli to their fingertips performed as well as when intracortical microstimulation (ICMS) of S1 was applied instead (Romo, Hernandez et al. 1998; Romo, Hernandez et al. 2000; Cohen and Newsome 2004). Recent research has demonstrated that spatiotemporal patterns of ICMS of S1 can not only provide feedback about reaching movements, but can also cue the direction of cursor movements controlled by recorded motor cortex neurons (Fitzsimmons, Drake et al. 2007; O’Doherty, Lebedev et al. 2009). These results indicate the possibility of bi-directional communication between the brain and neuroprosthetic device by using chronic multi-electrode recordings of motor cortex and ICMS of S1.

Though electrical microstimulation has been a powerful tool in clinical neuroscience and electrophysiology, it has numerous limitations including poor long term reliability due to the tissue reaction to the implanted electrodes, limited cell specificity, and low spatial resolution.

The main factors involved in the tissue reaction are the mechanical trauma caused during insertion, implantation method, foreign body reaction, and physical properties of the electrodes. As the electrode
is inserted into the cortex, it severs neuronal and glial processes, capillaries, and the extracellular matrix. This mechanical trauma creates a “kill zone” around the electrode and initiates an acute inflammatory and wound healing response (Landis 1994; Polikov, Tresco et al. 2005; Zhong and Bellamkonda 2008). The amount of trauma is related to the insertion speed, insertion site, and the size and shape of the electrode's tip (Edell, Toi et al. 1992; Szarowski, Andersen et al. 2003; Björnsson, Oh et al. 2006). In addition, long term stability is compromised by the chronic inflammation response of reactive astrocytes and microglia that results in degeneration of target neurons and electrode encapsulation (Landis 1994; Polikov, Tresco et al. 2005; Zhong and Bellamkonda 2008, McConnell, Rees et al. 2009). This encapsulation increases the tissue resistance which in turn affects the interface between electrodes and neurons (Turner, Shain et al. 1999). As a result, more charge is needed to get the same activation levels, which can lead to further damage to the tissue and electrode (Cogan 2008).

Limited cell specificity is due to non-selective depolarization of cell types, cell bodies, axons, and dendrites by the electrode’s complex electric field. Physical proximity to the electrode determines which cells will be stimulated and as a result it is difficult to discern the number and identities of the cells stimulated. In addition, currents may have different effects on neurons and fibers: they can result on activation or inactivation and they can elicit antidromic and orthodromic propagation in fibers. For example, side effects and therapeutic effects of electrical based therapies such as deep brain stimulation are difficult to discriminate due to the uncertainty of which neural elements are being excited (Kuncel and Grill 2004; Aravanis, Wang et al. 2007). The limited cell specificity of electrical microstimulation could be overcame with nanostimulation, a single-cell stimulation method derived from juxtacelullar labeling (Houweling, Doron et al. 2006). A single cell can be stimulated by bringing a fine glass micropipette in contact with the cell and applying current in the nanomillivolt range. Nanostimulation has already been used to stimulate single somatosensory neurons in awake head-fixed animals for behavioral studies (Voigt, Brecht et al. 2008; Houweling, Brecht et al. 2008). However, using this technique to stimulate several cells in freely moving animals will be very challenging. Although nanostimulation has the potential to provide high spatial resolution, it does not provide good temporal resolution as both studies reported long reaction times.

Spatial resolution of electrical microstimulation depends on the spread of the electric field, the threshold of activation of the cells within this field, and discharge rate. In addition, the physical properties of electrodes and their interaction with the tissue are a factor that influences spatial resolution and stimulation selectivity. Important factors affecting spatial resolution include inter-electrode spacing, geometry, contact location, contact orientation, charge density, pulse width, frequency, amplitude, and stimulation waveforms (Kuncel and Grill 2004; Cogan 2008; Grill, Norman et al. 2009).

It is clear that electrical stimulation of neural tissue has many disadvantages and limitations, demonstrating the need for a stimulation paradigm that is non-invasive, has high spatiotemporal precision, and remains viable over a long period of time. To this end, we propose a novel optical neural interface for spatiotemporally precise patterned activation of genetically modified neurons. Emerging optogenetic tools such as channelrhodopsin-2 (ChR-2) have the potential of long-term reliability, cell-specificity, and fast kinetics. These tools have already been used to activate neuronal circuits in a multitude of preparations.

ChR-2 is a non-selective cation channel, found in the green alga Chlamydomonas reinhardtii, that induces temporally precise depolarization of the membrane when activated with ~480nm light at light intensities as low as 1mW/mm² (Nagel, Szellas et al. 2003; Boyden, Zhang et al. 2005, Arenkiel, Peca et al. 2007). ChR-2 can be used to drive precise and sustained naturalistic trains of spikes with light frequencies of 5-50 Hz and pulse durations of 5-15ms as well as with Poisson-distributed series of light pulses (Boyden, Zhang et al. 2005; Itohizuka, Kakuda et al. 2005; Aravanis, Wang et al. 2007). Expression of ChR-2 does not affect membrane resistance, resting potential, number of spikes evoked, or cell death (Boyden, Zhang et al. 2005). This protein can be readily expressed in neurons using viruses, transfection, and transgenic methods in dissociated cultures, acute slices, and in vivo
Several groups have demonstrated potential uses of optogenetic methods in neuroprosthetic devices in a variety of in vivo studies. Evoked whisker deflections in rat demonstrated optical control of motor output by photostimulating the rat vibrissal motor cortex (Aravanis, Wang et al. 2007). Mouse studies have demonstrated that photostimulation of barrel cortex in a detection task can be associated with a reward (Huber, Petreanu et al. 2008). Millisecond-timescale optical control of neural activity was recently observed in the cortex of non-human primates (Bernstein and Han et al. 2008; Han, Qian et al 2009). All these studies also demonstrate the feasibility and safety of genetically modifying neurons in mammals.

Advances in genetic targeting are needed to develop a stimulation method with high spatial precision. Being able to target any cell in the somatosensory cortex would greatly enhance somatosensory feedback. For example, the specific line of transgenic mice that will be used in this proposal has homogeneous distribution of ChR2-YFP fusion protein throughout the tufted layer-5 neurons of the sensorimotor cortex (Ayling, Harrison et al 2009). Another group successfully introduced ChR2-GFP into a small fraction of layer 2/3 neurons of mouse S1 (Huber, Petreanu et al. 2008). Further understanding of the genetic structural and cellular architecture of the brain will allow targeting the enormous variety of cell types found in the central nervous system. To this end, The Allen Brain project has started a global analysis of gene expression in the mouse brain, which will serve as a baseline data set for comparison with other species (Lein, Hawrylycz et al. 2007). However, it is not clear how much these data set will translate to higher-order species. Several other groups are developing genetically targetable neural modulation tools including promoter based targeting with Thy1 and CaMKIIα, Cre lines, developmental targeting of specific cortical layers, and intracellular targeting motifs (Gradinaru, Thompson et al. 2007).

Another major challenge of an optical neural interface is the manner by which photons are delivered to the tissue. Several groups have already begun engineering optical neural interface devices for in-vivo light delivery. The simplest system involves a very powerful blue LED coupled to a thin (200-50um) flexible fiber optic for low-cost localized light delivery (Aravanis, Wang et al. 2007; Campagnola, Wang et al. 2008). Other groups are integrating optical stimulation with spatiotemporal recording by coupling the fiber optic set-up with an array of recording microelectrodes (Han, Qian et al 2009, Zhang, Laiwalla et al. 2009). Since a single fiber optic coupled to a single LED is incapable of providing patterned stimulation, a group developed a 10x10 LED array coupled to a multicore optical fiber of ~600um diameter to provide spatiotemporal patterned photostimulation (Xu, Davitt et al. 2008). However, fiber optics only emit light at the tip resulting in significantly less tissue being illuminated compared to the amount of tissue damaged during the insertion. To overcome this limitation, a 3-D array of LEDs in which a linear array of compact LEDs encased along glass capillaries and arranged in a vertical grid was developed to activate neurons distributed in a volume of tissue (Bernstein and Han et al. 2008). Although this device is capable of delivering light at multiple 3-D locations within the brain, it is potentially more invasive than an electrode array.

Although these devices represent first attempts at developing optical neural interfaces, there is still a need for non-invasive, flexible, and spatiotemporally precise devices capable of eliciting patterned activation. We propose to use Organic Light Emitting Diodes (OLEDs), which are different from traditional LEDs in that their emissive electroluminescent layer is composed of a thin film of organic polymers or small organic molecules. These organic compounds allow the design of easily customizable, flexible, and ultra-thin displays with extremely high resolutions and temporal responses.

Organic electroluminescence is the generation of light from an organic layer in response to an electric field generated by two surrounding electrodes. In specific, a thin cathode layer (~0.1-0.5um) injects electrons into the electron transport layer (ETL) while a transparent anode (~0.1-0.3um) injects...
holes into the hole injecting layer (HIL), which in turn injects the holes into the hole transport layer (HTL) (Friend, Gymer et al. 1999; Kafafi 2005). Then, light is generated when holes and electrons recombine at the emitting layer (EL), which is located at the boundary of HTL and ETL. In addition to the thin electrode layers, the organic layer is in the order of nanometers making the device very thin and light-weight (Kafafi 2005).

In contrast, inorganic LEDs do not have ETL, HIL, or HTL layers but have a valence band, a band gap, and a conduction band. When an electric field is applied, the electrons need to overcome the energy in the band gap to be able to move from the conduction band to the valence band where they recombine with the holes and produce a photon (Van Zeghbroeck 2007). In addition, there is a strong coupling between neighboring atoms due to covalent bonding in inorganic LEDs. In contrast, the molecules in OLEDs are held together by weak van der Waals forces, which allows them to be flexible.

In addition to being thin, light, and flexible, OLEDs have low carrier mobilities, which increase the probability of recombination due to high local charge density (Friend, Gymer et al. 1999). They also have high fluorescence efficiencies, high resolution (=Sum pixel size), fast switching (1-10us), and color tuning throughout the entire visible spectrum (Bardsley 2004; Kafafi 2005). They also exhibit an almost perfectly linear relationship between brightness (Cd/m²) and OLED current (Kafafi 2005).

The purpose of this research is to develop a technique that will overcome the limitations of the microstimulation methods that are currently used for neural modulation: poor reliability in chronic settings, limited cell specificity, and low spatial resolution. ChR-2 provides a method for long term reliability: once the protein is part of the DNA, the target cell will always express the protein. In addition, limited cell specificity and low spatial resolution can be overcome with the potential of genetically targeting any type of cell. Finally, the thin, light, and flexible OLED display will provide a tool for non-invasive patterned stimulation. OLEDs also provide a method for long-term reliability since the use of light avoids the need for direct physical contact with the tissue.

C. Preliminary data

In my preliminary experiments I was able to use OLEDs to elicit small currents in ChR-2 neurons in dissociated cultures and to develop a stimulation-response relationship of the peak and steady state photocurrents. In this experiment I used calcium phosphate transfection to express Thy-1-ChR2/EYFP in wild type neurons. Here, Thy-1 is used as the promoter to drive expression of ChR-2 in neurons that have the Thy-1 protein. Thy-1 is present on a fraction of brain cells mainly found in the striatum, hippocampus, neocortex, and cerebellum. In addition, the fusion of ChR-2 protein to Enhanced Yellow Fluorescent Protein (EYFP), allows us to visually find a ChR-2-positive cell by locating neurons that fluoresce green. After the transfection of a subset of neurons, I visually targeted and patch-clamped a positive cell using standard whole-cell voltage-clamp techniques. To verify that the visually identified ChR-2:EYFP positive cell was the patched cell, I used a fluorescent dye (Alexa 568, Fig. 1A). For the experiment, I used an OLED array with an emission spectrum centered at 450nm. As a positive control, I used the mercury lamp of the confocal microscope through the 480+/− 10 nm filter cube.

Light stimulation of the patched cell with the OLED and mercury lamp elicited photocurrents that lasted as long as the light was on: four seconds and two seconds, respectively (Fig. 1B). I drove the OLED with different currents ranging from 50mA to 500mA while recording the peak and steady state photocurrents. Both the peak and steady state currents were dependent on the OLED driving current (Fig. 1C).
Figure 1: OLEDs stimulate ChR-2 mediated membrane currents in ChR-2 expressing dissociated cortical neurons. (A) A ChR-2: EYP positive dissociated neuron is shown whole-cell voltage-clamped and filled with Alexa 568. (B) The top current trace illustrates a ChR-2 mediated membrane current, which was activated by an OLED. The bottom trace shows the photocurrent elicited by a BP-filtered mercury lamp. (C) Scatter plot illustrating ChR-2 current amplitudes as a function of OLED drive current.

In addition, I was able to use calcium imaging to detect light-evoked activity in ChR-2 dissociated cultures. In this experiment, I used Rhod-2-AM, a high affinity long-wavelength calcium indicator with excitation and emission maxima at 552 nm and 581 nm, to load wild type and transfected dissociated cells. Using high resolution time-lapse confocal imaging, I recorded the increase in fluorescence due to influx of calcium. As a control, I recorded the spontaneous increase in fluorescence of wild type neurons (Fig. 2B). Using the confocal's blue laser, I stimulated a section of loaded cells that contained a single ChR-2 positive neuron (Fig. 2A). Upon analysis of a ChR-2 negative cell and the ChR-2 positive cell, I observed an increase in fluorescence during the light stimulation (Fig. 2C). The red trace in Figure 2C represents the change in fluorescence at the cell body of the ChR-2 positive cell when the blue laser was on for 31 seconds. The green trace is from a ChR-2 negative cell located just above the positive cell.

Figure 2: ChR2-mediated calcium activity. (A) Left: Dissociated neurons loaded with Rhod-2-AM. Center: ChR-2: EYP positive dissociated neuron. Right: Merging of the two images. (B) Spontaneous activity from 3 wild type cortical dissociated neurons that was recorded for 125 seconds with time-lapse confocal imaging. Trace shows absolute change in fluorescence after background and prestimulus baseline were subtracted. (C) Absolute change in fluorescence recorded from one ChR-2 neuron (red trace) and one ChR-2 negative cell that were all stimulated with the blue laser for 31 seconds.
As an initial attempt at activating ChR-2 cells in acute slices, I was only able to evoke activity when using the band-passed mercury lamp and not the OLED. After visually locating ChR-2 positive pyramidal cells in layer 5 of Thy1-ChR2/EYFP transgenic mice brain slices (Fig. 3A), I voltage-clamped and recorded the evoked photocurrents from one cell while using both light sources separately. Though the mercury lamp succeeded in eliciting photocurrents (Fig. 3B), the OLED was unable to elicit detectable currents. A possible reason why we did not detect photocurrents may have been light scattering and attenuation. Since the patched cell was located close to the surface and the OLED was located at the bottom of the slice, the light from the OLED had to go through ~300um of tissue while the light from the lamp came from above the tissue. Therefore the light intensity at the target cell was different for each light source. Increasing the driving current of the OLED to increase the light intensity created an electrical artifact that disrupted the giga-ohm seal of the patched cell.

Another possible reason why we did not observe photocurrents was that the OLED's emission spectrum was very narrow and might not be aligned with the ChR-2's excitation spectrum. As part of this proposal, I am proposing experiments that aim to measure photocurrents as a function of tissue thickness and OLED settings as well as determining the OLED’s peak emission wavelength that will maximally activate a ChR-2 neuron.

Figure 3: ChR-2 stimulation in acute slices of cortex. (A) Left: low magnification image of the recording location in layer 5 of Thy1-ChR2-EYFP transgenic mice cortex. Right: higher magnification image of a ChR-2:EYFP positive pyramidal neuron filled with Alexa 568. (B) ChR-2-mediated membrane current elicited by 1.5 seconds of light stimulation with a mercury lamp.

D. Research Design and Methods

Aim 1: Determine the best OLED parameters to activate ChR-2 neurons

Rationale

To determine the optimal OLED parameters that effectively activate one ChR-2 neuron, I propose a series of electrophysiological experiments that will characterize the response properties of ChR-2 neurons to different OLEDs settings. To determine what basic light mediated OLED characteristics (size, current needs, light intensity, peak emission wavelength, light pulse duration, and frequency of light pulses) best induce channel activation, I propose to measure the voltage and current responses of ChR-2 neurons using dissociated cultures. The monolayer of cells in dissociated cultures will limit the light scattering and absorption, allowing me to easily characterize these different properties of OLEDs when used to activate a ChR-2 neuron. In addition, these cultures can be easily transfected with chemical methods. Transfecting wild-type neurons results in lower density and faster expression of the protein. Low expression density results in reduced background fluorescence, which is better for imaging. However, the monolayer of dissociated cultures does not provide the tissue thickness and neuroanatomy that a neurodevice will experience. As a result, acute slices also need to be investigated.

To determine the effects of cortical tissue thickness on the ability of the light to activate the light-sensitive channels in a volume of tissue, I propose performing experiments using acute brain slices to measure how much the photocurrents decrease with increasing thickness. These slices have greater mechanical stability and allow for greater control of the extracellular environment than other in vivo and in vitro preparations. Acute slices retain neuronal connectivity and cell-matrix interactions that dissociated cultures lack. Additionally, acute slices can be prepared and used in the same day.

Both the dissociated cultured cells and acute slices come from homozygote Thy1-ChR2/EYFP mice. I will also culture and transfect neurons from wild-type mice with a Thy1-ChR2/EYFP plasmid. To
Electrophysiology and Optical Methods

We will use an upright electrophysiological microscope to image the cells from the top while stimulating the cells from the bottom of the chamber. The OLED display will be set up under the recording chamber that will be holding the cultures and slices. The bottom of the chamber is optically clear and should not interfere with the OLED optics. A 16x water-immersion lens and a YFP-filtered white LED light will be used to visually locate the ChR2:EGFP cells. Twice as much magnification will be used during patch-clamping. The internal solution will be composed of Alexa 568 and cesium gluconate, which provides better space clamping. 
Pclamp 10 software and Clampfit (Axon Instruments) will be used to record and analyze the peak current, steady state current, and spiking elicited by the OLED. For a negative control I will test the OLED on wild type and YFP neurons. The YFP-filtered white LED will serve as a positive control to activate the ChR2 cells, while wild-type and YFP neurons will serve as negative controls.

1.1 To determine the effective intensity of the OLED.

In order to determine the intensity necessary to maximally activate one ChR2 neuron, I will vary two parameters that directly relate to intensity: OLED size and current supplied to the device. An OLED with a smaller active area and higher power might elicit the same response from a cell as a larger OLED with less power. Therefore the goal of this experiment is to find the effective intensity where the combination of current supplied and OLED size effectively activates one cell. To this end, I will vary these two properties based on the manufacturer specifications. The resolution of the device is 160x128 pixels and has an active area of 33.6mm x 27mm, which results in a pixel every 0.21mm. I will increase the OLED size from one pixel to where the imaged area is completely illuminated while recording the cell's evoked response to every increment. Concurrently, I will vary the current supplied from 10mA to 115mA. In order to study the effect of each factor and interactions between the factors, I will use a multi-level two-factor full factorial experimental design with 2 factors (size, current) and 4 levels each. This design will allow me to reduce confounding effects by setting up the combinations of current and OLED size and the order in which I apply them. If the number of levels does not give me enough information to determine optimal OLED parameters, I will increase the number of factor levels. 

If the number of combinations becomes too high to be feasible, I will use a fractional factorial design. In this type of design, it is assumed that high-order interactions are negligible and thus running only a fraction of the complete experiment will provide enough information on the main effects and low-order interactions (Montgomery 2009). Then I will use an ANOVA to analyze the results. In addition, I will measure the intensity of light exiting the OLED with a photodiode for every factor level combination to determine a relationship between light intensity and evoked activity.

1.2 To determine the OLED's peak emission wavelength

To determine the OLED wavelength that will maximally activate a ChR2 neuron, I will use different wavelengths of blue light to elicit photocurrents. Since the OLED module allows me to choose from 65,536 colors, I will vary among different types of blue while recording the cell responses. The size of the increments will depend on the number of blues that are available to choose from in the OLED's library of colors. Once I find a set of blues, I will measure their wavelength with a spectrometer. Since ChR2 responds maximally somewhere between 460nm and 480nm (depending on pH, Nagel, Szellas et al. 2003), I will use a set of blues whose wavelengths vary from 410nm to 530nm.

1.3 To determine the OLED's temporal resolution

The goal of this experiment is to determine the ability of the OLED to control neuronal spiking in a millisecond timescale. These experiments will tell us how fast we can drive the OLED and still elicit
precisely and reliably timed spikes. I propose varying the frequency and duration of the light pulses while measuring the cell's response. I will use a range of frequencies from 5Hz to 40Hz at 5Hz intervals, which corresponds to the frequency range used to elicit the sensation of flutter (Romo, Hernandez et al. 2000). In addition, it has been reported that ChR-2 responses significantly decline beyond 30Hz or 50 Hz (Boyden, Zhang et al. 2005; Ishizuka, Kakuda et al. 2005). Similarly, I will vary the light pulse durations from 1ms to 35ms with increments of 5ms, which is what has been reported in the literature (Boyden, Zhang et al. 2005; Ishizuka, Kakuda et al. 2005). In order to simultaneously test these two factors, I will use a multi-level two-factor full factorial experimental design with two factors (frequency, pulse duration) and eight levels each. Then I will use an ANOVA to analyze the results.

1.4 To determine the effects of cortical tissue thickness

The goal of this experiment is to determine the effects of cortical tissue thickness and how much power the OLED needs in order to effectively activate ChR-2 cells deep in tissue. As explained before, I will set the OLED on the bottom of the slice and patch a cell located at the surface, so light will travel through the various tissue thicknesses to reach the patched cell. Since there will be attenuation of the light intensity as it travels through the tissue layers, the intensity of light exiting the OLED will not be the same at the cell level. First, I will determine the attenuation of light by using the OLED settings determined during the experiments pursued in Aim 1.1 by recording from a cell located at the very surface of the slice. I will increase the thickness of the slices from 100um to 500um in 50um increments. This will also provide evidence of the resolution of the attenuation. Having determined the resolution of attenuation and effective intensity of the OLED, I will vary the current supplied, OLED size, and slice thicknesses to determine a combination that effectively overcomes the attenuation. I will use a multi-level three-factor full factorial experimental design with three factors (current, size, slice thickness). The recordings in dissociated cultures will serve as a control.

Expected outcomes and potential pitfalls of Aim 1

These experiments should reveal the potential of OLEDs to target and drive ChR-2 cells in vivo in a pattern of activity. After determining the optimal OLED settings to drive a specific cell at a specific depth, I should be able to design an array to drive many cells in a pattern. Specifically, I expect that the smallest OLED size will be able to elicit photocurrents, but it might need significant power to do this. If our current OLED system is not powerful enough to do this, we would need to find a more powerful commercially available OLED system. I also expect that a shade of blue close to 480nm in wavelength will maximally activate ChR-2 neurons. I further anticipate that the OLEDs will behave similarly to other light sources and thus will show similar temporal resolutions. Although slices are more complex preparations, I expect that the OLED will have enough intensity to elicit photocurrents in the acute brain slices.

A problem I may encounter is differentiating between light-evoked and synaptically evoked spiking activity. Using pharmacology, we would be able to reduce synaptic activity such as increasing the extracellular concentration of MgCl and CaCl or by blocking NMDA and AMPA currents with APV and NBDX. Another problem I may encounter is evoking action potentials due to cesium gluconate blocking the potassium channels of the neurons. To overcome this potential problem, I would switch the intracellular solution to potassium gluconate, which does not block potassium channels.

Another potential problem I may encounter is an electrical artifact induced by the OLED's proximity to the tissue. I observed artifact currents during my preliminary experiments that obscured the photocurrents and even disrupted the patch when the intensity of the light or the pulse duration was increased. This effect could be reduced by increasing the air gap between the OLED and the chamber, however it may be a better solution to insulate the surface of the OLED with an insulating coating that would not interfere with the optics.
2. **Aim 2: Prototype and test an OLED array to drive a group of cells in a pattern of activity**

**Rationale**

The rationale behind this aim is to design an OLED display that is able to activate cells in patterns of activity with high temporal and spatial resolutions, which are desired characteristics for neunromodulation. The objective is to design an OLED that can not only activate cells *in vitro* but could potentially activate cells *in vivo*. To this end, I will use the knowledge gained from the proof-of-concept experiments performed in Aim 1 to design and test a functional OLED display. Specifically, I will record the sequential activation of many cells while trying different arrangements and spacings of the individual OLEDs that will form the array. Although electrophysiological approaches provide a direct measurement of electrical signals with high temporal resolution and signal-to-noise ratio, they do not provide simultaneous monitoring of the activity and spatial location of a population of neurons. Therefore, I will employ optical recording methods to detect the light-evoked activation from the neuronal population.

To verify and validate that the measurements in Aim 2 are consistent with those in Aim 1, I will perform an intermediate experiment. In this experiment I will simultaneously record the light-evoked activity from a ChR-2 neuron simultaneously with electrophysiological and optical recording methods. In specific, I will use calcium indicators to optically monitor neuronal activity, which can be achieved either with calcium-sensitive fluorescent indicators or genetically encoded calcium probes. For the proposed experiments, I will use Rhod-2-AM, a high affinity long-wavelength calcium indicator with excitation and emission maxima at 552 nm and 581 nm. Based on my preliminary data, excitation of Rhod-2-AM does not activate ChR-2 neurons and accurately displays an increase in fluorescence with blue light stimulation. High-affinity calcium dyes produce large and easily detectable signals. However, they act as buffers to intracellular calcium and thus report calcium signals with slower kinetics. Although temporal resolution is better in low-affinity dyes, they have much smaller signals that are not as easy to detect. In addition, long-wavelength excitation induces less photobleaching and phototoxicity and also penetrates deeper in brain tissue. For the analysis, I will subtract the background fluorescence and then measure the absolute change in fluorescence.

**2.1 To determine conceptual connectivity between Aim 1 and Aim 2**

The goal of this experiment is to validate the optical measurements by determining a relationship between electrical signals and increase in fluorescence. To this end, I will measure and compare the latency, transient response, and time constant of the electrical and fluorescence signals evoked with light. Using dissociated cultures, I will patch a Rhod-2-loaded ChR-2-positive cell and simultaneously record the current-clamped activity and calcium transients. For the light stimulation, I will use the OLED settings determined during the experiments pursued in Aim 1. To verify that the ChR-2 channel is functional and ChR-2 activation is inducing calcium transients, I will switch to voltage clamp to record the photocurrents.

**2.2 To activate cells in a pattern of activity**

The goal of this experiment is to design an array with OLEDs that could discretely activate cells in a sequence. To design this array, I will use the OLED's software and the OLED parameters determined in Aim 1.1 and Aim 1.2. I will use 2x1, 2x2, 4x2, and 8x2 OLED arrangements to get discrete and sequential activation of different ChR-2 cells. To carry out the experiments, I will time-lapse images dissociated cultures loaded with Rhod-2-AM while discretely stimulating ChR-2 neurons with different OLEDs in the array. I will only use dissociated cultures for this experiment in order to limit network connectivity and light scattering.

**2.3 To determine the specifications of the OLED array**

The goal of this experiment is to determine the proximal spatial placement of OLEDs without activating more than one cell per OLED. Using dissociated cultures, I will find two adjacent cells and
activate them with the array while recording the fluorescent intensity. I will try different spacings until I find the minimum distance between two OLEDs that will still discretely activate two ChR-2 cells. I will use spacings varying from 0.21mm to 1mm apart.

2.4 To validate the OLED array by playing patterns in slices
The goal of this experiment is to discretely activate cells in a pattern when the cells are in a physiologically relevant environment; that is, there is a layer of tissue separating the device and the network of cells. As in 1.4, I will validate the results obtained from the monolayer cultures by using the OLED display on acute brain slices. I will use the same arrangements of OLEDs as in Aim 2.2. Additionally, I will use pharmacology methods as outlined in Aim 1 to limit synaptic activity among the activated cells.

Expected outcomes and possible pitfalls of Aim 2
Performing an intermediate experiment to conceptually connect Aim 1 and Aim 2 will allow me to verify and validate that the measurements in Aim 2 are consistent with those in Aim 1. I anticipate that the current-clamp measurements of the spontaneous and light-evoked activity will show minimal lag between the membrane depolarization and increase in fluorescence. However, I expect to see a temporal resolution mismatch due to electrical signals being very fast and calcium transients lasting longer than action potentials. This could be improved by increasing the scanning rate of the camera or using a low-affinity dye, which will result in shorter transients. However, the amplitude of the calcium signal is smaller with low-affinity dyes. For the voltage-clamp measurements of spontaneous activity, I anticipate no change in fluorescence intensity since a voltage-clamped cell will not fire and thus will not have an influx of calcium. Similarly, I anticipate no detectable change in fluorescence intensity in a voltage-clamped cell stimulated with light because the calcium influx through the ChR-2 channel may not be large enough.

Another issue with optical imaging is that the number of measured photons is significantly less than the number of measured electrons. If the number of photons detected is sufficiently low, then shot noise arises. Shot noise is due to the statistical nature of photon emission and detection resulting in fluctuations around the mean in the number of photons emitted per time, which reduces signal-to-noise ratio (Baker, Kosmidis et al. 2005; Scanziani and Hausser 2009). In order to improve signal-to-noise ration, I could increase the illumination intensity or decrease the concentration of the dye. Finally, other problems with optical recordings include light scattering and out of focus light. This could be improved by using a confocal or 2-photon microscope. However, signal to noise ratio will drop due to the decrease in number of photons detected.

I anticipate that these experiments will result in an OLED array capable of activating ChR-2 cells in complex patterns of activity. Specifically, I expect that a simple pattern and arrangement will have no problem activating different cells. However, I expect to have some difficulties eliciting discrete activation when using a more complex arrangement. These difficulties could arise from the design itself and/or from the cells. It is impossible to know how the positive cells are going to be arranged relative to one another before the start of the experiment, and therefore it will be somewhat difficult to align the OLEDs to each cell. One possible solution is to quickly design the arrangement of the OLEDs after inspecting the cells under the microscope at the beginning of the experiment. This solution is dependent on the complexity of the software. Another solution is to use cultures that have different expression densities. Cultures made from transgenic mice will have higher densities of ChR-2 cells than transfected cultures. I will use both to determine the best concentration of ChR-2 cells.
E. References Cited


SUBSEQUENT EXPERIMENTS AND WORK

The studies completed before the prospectus, which are presented under the preliminary data section, relied on devices from the Flexible Design Center at Arizona State University. One of these devices is shown in Figure 1A. Unfortunately, the collaboration with the center ended before I could start the proposed experiments. Therefore, the following studies were performed with an OLED display we purchased from 4D Systems (Sydney, Australia), which is shown in Figure 1B. To make sure the new device provided the same wavelength as the previous device, we measured their emission spectra. Figure 1C shows the emission spectra for each of the devices, which highlights that the peak wavelength was similar for both devices: 460nm.
Figure 1. OLED devices and their corresponding emission spectra. (A) An array of “blue” OLEDs containing five distinct OLEDs is shown. Copper-based tape leads were used to connect the OLEDs to a DC power source. OLEDs were then mounted underneath a standard slice-recording chamber. An illustrator of the final OLED stimulation chamber is illustrated in the right-hand panel. (B) Commercially available OLED display module from 4D Systems illustrating the capability of multicolored patterned activation. The module was mounted underneath a standard slice-recording chamber and powered through a USB cable. (C) Left-hand panel: emission spectra of OLED array. Right-hand panel: emission spectra of the OLED display for nine different colors.
The next step was to replicate the experiments in vivo. The goal of this study was to be able to elicit paw movements by stimulating over motor cortex with a light source. To this end, Thy1-ChR2/EYFP transgenic mice were anesthetized with ketamine-xylazine cocktail, which was injected i.p. The level of anesthesia was carefully monitored and maintenance doses were given as needed. The head was placed in a stereotactic rig and the fur was sheared from the top. A midline scalp incision was made and a 1mm craniotomy was drilled over the left motor cortex. Two light sources were used for the experiment and placed over the craniotomy: the OLED display and a blue laser coupled to a fiber optic. The optical stimulation parameters for the laser were: 0.5sec pulses were applied to the craniotomy at 1-2 Hz. Video recording was done at 30 frames per second.

As an initial attempt at activating ChR-2 cells in vivo, we were able to elicit repetitive paw movements when stimulating with a blue laser coupled to a fiber optic. Figure 2 shows the lightly anesthetized mouse mounted on a stereotactic frame before and during light stimulation. Both paws are marked with crosses to show the paw displacement. Panel (a) shows the mouse before one pulse of blue light, which lasted approximately 0.25 seconds. Panel (b) shows the mouse during one pulse of light stimulation. This figure also shows paw displacement upon light stimulation.

Figure 3 shows frame-by-frame of the mouse before, during, and after light stimulation. We observed that the left paw twitched upwards during light stimulation and then returned to normal with conclusion of the stimulation. Panels (a) and (b) show the mouse before light stimulation and
the paw in a resting position. Panels (c)-(i) show paw displacement during one pulse of light stimulation, which lasted 7 frames. We observed that it took a couple of frames before the paw movement was noticeable and the paw continued in the upward position for the duration of the light stimulation. Panels (j)-(n) show the paw after light stimulation was stopped. We observed that the movement did not stop immediately with conclusion of light stimulation. It took a couple of frames after light stimulation was stopped for the paw to return to a resting position.

Figure 2. Blue light stimulation of left motor cortex in Thy1-ChR-2/EYFP adult mice induced repetitive paw movements. (a) Lightly anesthetized mouse mounted on stereotactic frame before light stimulation. (b) Same mouse during light stimulation that induced the left front paw to twitch.
Figure 3. Frame-by-frame image of 0.5 seconds of recording when the left motor cortex in Thy1-ChR-2/EYFP adult mice was stimulated with one pulse of blue light. (a)-(b) two frames immediately before light stimulation. (c)-(i) seven frames of light stimulation. (j)-(n) five frames immediately after light stimulation.

DISCUSSION

We have demonstrated that it is feasible to use OLEDs to stimulate ChR-2 expressing neurons. We have demonstrated this basic principle in both dissociated neurons, as well as in the light scattering tissues of acute slices. As an initial attempt at activating ChR-2 cells in vivo, we were able to elicit repetitive paw movements when stimulating the left motor cortex through the skull with a blue laser coupled to a fiber optic. However, in vivo stimulation of ChR-2 neurons requires powerful enough OLED displays. The minimum light luminance necessary to activate ChR-2 cells is in the range of $10^6 \cdot 10^7 \text{ cd m}^{-2}$ (Grossman et al., 2010), which is easily achieved with
high power light sources such as arc lamp, lasers, and high power LEDs.

However, commercially available OLED displays are diffused sources of light with light luminance in the range of 250-1000 cd m^-2.

FUTURE DIRECTIONS

An OLED array could be used as a part of a cortical neuroprosthesis to elicit a variety of sensations regarding touch and pressure to the somatosensory cortex. Sensors embedded in the finger of a prosthetic hand could be used to gather and process somatosensory information and pressure responses to a microprocessor, which in turn sends patterns of activity to the OLED matrix to then activate somatosensory cortex in order to provide smart tactile feedback from the prosthetic hand. The OLED matrix would thus activate ChR-2 expressing neurons and circuits in specific patterns to elicit specific sensations.

Achieving this goal requires the use of powerful and flexible OLEDs that are capable of patterned activation.
BIOGRAPHICAL SKETCH

Liliana Rincon Gonzalez was born in Bogota, Colombia. She immigrated to the United States to attend college where she received both a B.S.E degree in Bioengineering and a B.A. in Psychology from Arizona State University in 2007. In 2010 she received a M.S. degree in Biomedical Engineering from Arizona State University. She just completed a doctorate in Biomedical Engineering at Arizona State University, where her research involved the analysis of the stability and calibration of the internal representation of arm position.