Upper limb proprioceptive sensitivity in three-dimensional space: effects of direction, posture, and exogenous neuromodulation

By

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ABSTRACT

Proprioception is the sense of body position, movement, force, and effort. Loss of proprioception can affect planning and control of limb and body movements, negatively impacting activities of daily living and quality of life. Assessments employing planar robots have shown that proprioceptive sensitivity is directionally dependent within the horizontal plane however, few studies have looked at proprioceptive sensitivity in 3d space. In addition, the extent to which proprioceptive sensitivity is modifiable by factors such as exogenous neuromodulation is unclear. To investigate proprioceptive sensitivity in 3d we developed a novel experimental paradigm employing a 7-DoF robot arm, which enables reliable testing of arm proprioception along arbitrary paths in 3d space, including vertical motion which has previously been neglected. A participant's right arm was coupled to a trough held by the robot that stabilized the wrist and forearm, allowing for changes in configuration only at the elbow and shoulder. Sensitivity to imposed displacements of the endpoint of the arm were evaluated using a "same/different" task, where participant's hands were moved 1-4 cm from a previously visited reference position. A measure of sensitivity (d') was compared across 6 movement directions and between 2 postures. For all directions, sensitivity increased monotonically as the distance from the reference location increased. Sensitivity was also shown to be anisotropic (directionally dependent) which has implications for our understanding of the planning and control of reaching movements in 3d space.

The effect of neuromodulation on proprioceptive sensitivity was assessed using transcutaneous electrical nerve stimulation (TENS), which has been shown to have beneficial effects on human cognitive and sensorimotor performance in other contexts. In this pilot study the effects of two frequencies (30hz and 300hz) and three electrode configurations were examined. No effect of electrode configuration was found, however sensitivity with 30hz stimulation was significantly lower than with 300hz stimulation (which was similar to sensitivity without stimulation). Although TENS was shown to modulate proprioceptive sensitivity, additional experiments are required to determine if TENS can produce enhancement rather than depression of sensitivity which would have positive implications for rehabilitation of proprioceptive deficits arising from stroke and other disorders.

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CHAPTER 1 INTRODUCTION

Overview of Proprioceptive Function

Proprioception comprises the senses of body position, movement, force, and effort. This sense is extremely important for typical functioning and movement. This sense greatly contributes to activities of daily living (ADLs) such as tying your shoes, walking without having to watch your feet, and picking up a glass of water among many, many other activities.

Anatomy and Physiology

Proprioceptors

Any change in the configuration of a limb can activate proprioceptive receptors in joints, muscles, and skin. The main contributor towards proprioceptive sensation are the muscle spindles that are found in capsules within muscles although Golgi tendon organs as well as stretch receptors also contribute (Proske & Gandevia, 2012). There are different types of fibers within the capsule that are responsible for different components of the spindle response. A diagram of these fiber types can be found in Figure 1. Type 1a afferent fibers send signals related to the dynamic changes of the muscle as an indication of when muscle length is changing, and the rate of the discharge is correlated with the velocity of the change. These 1a fibers split within the capsule and form annulospiral endings around the centers of bag 1, 2 and chain fibers. Bag 1 and 2 fibers have a fusiform enlargement in the center that doesn’t contain any contractile units. Type 2 fibers also provide proprioceptive information but signal the length of the muscle. They produce flower like sprays in the bag 2 and chain fibers near the edge of the capsule and not around the fusiform center of bag fibers as 1a fibers do. With type 1a afferents providing dynamic information about current movement and the type II afferents providing length information the current position and active motion of the muscle can be calculated.

Another component of the muscle spindle is the gamma motor neuron enervation which helps to maintain a correct tautness in the spindle to provide continued sensitivity with muscle stretches and relaxations. The subtypes of gamma motor neurons are the dynamic and static. Dynamic gamma neurons enervate the Bag 1 fibers and, as the name states, provides dynamic input to tighten the fiber or allow it to relax to the have the correct tension for that moment. The static gamma neurons provide consistent firing to bag 2 fibers and chain fibers. These provide static input that provides some small amount of contraction and keeps the spindle taut with the muscle it is housed within but is not dynamically related to the activity of the muscle.

The Golgi tendon organ, joint receptors, and skin stretch receptors also contribute towards an overall proprioceptive sense. A diagram of these receptors can be found in Figure 2. Specifically, Golgi tendon organs are responsible for providing information about the amount of tension acting on a muscle. A Golgi tendon organ has attachments to approximately 10 muscle fibers from different motor units attached near the tendon. Between these connections and multiple Golgi tendon organs information about the muscle tension can be gathered.

Joint receptors contribution to large movements has been shown to be minimal and most likely act mostly as a limit detectors in joints. Although some evidence has shown their role to be more important in some mid-range motion of finger joints (F. J. Clark, Grigg, & Chapin, 1989; Ferrell, Gandevia, & Mccloskey, 1987).

Central Processing

After proprioceptive signals have been generated in the lower part of the body by the receptors they travel to the spinal column where they synapse onto Clarke's column (dorsal nucleus) in the spinal cord (Purves et al., 2012). Clarke's column then projects through this dorsal spinocerebellar tract into the cerebellum but also send collaterals to the dorsal column nuclei. Proprioceptive signals from the upper body project similarly but travel upwards through the fascilus cuneatus in the dorsal columns of the spinal cord and synapse in the dorsal column nuclei. Both nuclei then project to the thalamus via the medial meniscus. The ventral posterolateral nucleus (VPL) of the thalamus has projections that relay these signals into the cortex, typically the somatosensory and association cortices. A diagram showing the pathways responsible for conscious perception of proprioception can be seen in Figure 3. The figure doesn't include pathways to the cerebellum that project from the medullary nuclei into the cerebellum.

The cerebellum is involved in many processes of which coordinated and smooth motor movements are required. The proprioceptive information from the muscle spindles and Golgi tendon organ receptors is believed to be used to correct errors detected by comparing the expected outcome from forward model predictions (G. A. Apker, Karimi, & Buneo, 2011; Carrozzo, McIntyre, Zago, & Lacquaniti, 1999; R. J. van Beers, Sittig, & Denier van der Gon, 1998). This information is typically unconscious activity that helps to correct movement errors and adjust for perturbations caused by the outside world to more quickly adapt and reach intended goals.

Proprioceptive Function During Skilled Motor Behavior

Furthering our understanding of proprioception is important because of the ubiquitous use of proprioception in the performance of typical activities of daily living (ADLs), such as reaching, grasping, and manipulation, where it goes largely unnoticed.

Proprioception is typically imperceptible but still contributes to the planning and initiation of appropriate actions, coordinates joint motions during these actions, and assists in adapting motor plans to account for external perturbations. For example, reaching in the dark to find a light switch, picking up a glass that's out of view, or walking on an uneven surface requires proprioception to guide our movements and update our actions if the motion deviates from expectations (Park, Toole, & Lee, 1999; Scheidt, Conditt, Secco, & Mussa-Ivaldi, 2005). Impairment of our ability to feel the location of our body in space and the actions that we are taking dramatically impacts the planning and control of limb and body movement (Ghez, Gordon, & Ghilardi, 1995; Gordon, Ghilardi, & Ghez, 1995). In active reaching tasks it was shown that patients with large fiber sensory neuropathy, which results in a loss of sense of limb position, were unable to account for inertial aspects of limb motion and had difficulty coordinating activation between limb segments to smooth trajectories as well as to stop movement once a target had been reached. This resulted in inaccuracies in reaching a target location but also showed increased involvement of limb segment inertia in the final trajectory of the reaching motion (Gordon et al., 1995). Errors in this movement were also largely reduced by providing temporary vision of the arm to participants with proprioceptive deficits. Complete vision of the arm during movements allows for compensation of the lack of proprioceptive information. If vision is removed then estimates of starting limb position begin to accumulate errors causing reaching movements to become less accurate over time (Ghez et al., 1995). Proprioception is demonstrated to be critical, in the absence of vision, in maintaining state estimates of arm configuration for movement planning as well as for online corrections.

Contribution of Proprioception to Body Representations

The deft performance of motor activities is thought to at least in part depend upon proprioceptive contributions to 'embodiment', a term originally described as "body schema" in 1911 as a bottom up, unconscious, dynamic representation using proprioceptive information from muscles, joints, and skin (Head & Holmes, 1911). Body schema has been adapted over time for use in describing sense of ownership for prosthetics and to distinguish between perceptions of self, 'body image', and sensorimotor representations of the body that facilitate movement, 'body schema' (Maravita & Iriki, 2004; Vignemont, 2010). These terms still have overlap in use although there is evidence showing that disruption of one is possible without disruption of the other (Berti & Frassinetti, 2000). Embodiment is typically used as an extension of body schema that can extend or be altered with tool use, including prosthetics (Berti & Frassinetti, 2000; Garbarini et al., 2015). There is ongoing debate about the specific boundaries of these terms and the amount of overlap between them neurologically and functionally. Proprioception is specifically involved in body schema as it provides information about the configurations of joints in space which allows for planning of limb and body movements (Ghez et al., 1995; Gordon et al., 1995).

A classic experiment used to induce embodiment in an external object is the body transfer illusion or rubber hand illusion (Ehrsson, Spence, & Passingham, 2004). A rubber hand is laid out on a table while a participant puts one hand out of view, often behind a screen or in a box. The participant is asked to watch the rubber hand as an experimenter brushes the rubber hand and the participant's hidden hand simultaneously on the same locations with a paint brush. When asked to point at their hand many people would point to the rubber hand (Botvinick & Cohen, 1998; Ehrsson et al., 2004). Embodiment can alter a person's understanding of their body and seems to be a natural consequence of tool use. Even using a tool to extend the reach of an arm can lead to an overestimation of arm length (Garbarini et al., 2015). Incorporating external objects into our body schema, as shown by the rubber hand illusion, may allow for leveraging of predictive models. By incorporating proprioceptive information about changes in inertial as well as motor outcomes of actions while using those tools would allow for more accurate motor planning and compensation.

Robotic Assessment of Proprioception

Assessment of proprioceptive function in a clinical setting is still relatively crude despite it's important for normal sensorimotor functioning. Methodologies for assessing proprioception in a more robust way have been developed through the use of planar robotic exoskeletons (Dukelow et al., 2010). By using the robot to passively drive one arm to a target location and having a subject actively match that location gives information about proprioceptive sensation. These experiments can be done with active or passive movements that further illustrates the differences in information provided by different modalities of motion. These types of studies have also been used to test stroke survivors to measure movement detection threshold to robustly classify proprioceptive deficits (Simo, Botzer, Ghez, & Scheidt, 2014). Studies have also tested intact participants to better understand typical functioning and limits of proprioception (Cressman & Henriques, 2011; Dukelow, Herter, Bagg, & Scott, 2012; Dukelow et al., 2010; Fuentes & Bastian, 2010; Simo et al., 2014). Most of these have focused on movements in a single horizontal plane and have shown that sensitivity is dependent upon the position of the arm and the direction of movement on that plane. Recently, proprioception of the wrist has been tested and quantified in 3 dimensions of movement (abduction/adduction, pronation/supination, and flexion/extension) however similar testing of full arm motion has not yet been conducted (Marini et al., 2017). Reaching studies have shown that movements in directions within the vertical plane have kinematics that appear to be optimizing for both gravitational and inertial forces (Berret et al., 2008; Gentili, Cahouet, & Papaxanthis, 2007; Le Seac'h & McIntyre, 2007; Papaxanthis, Pozzo, & Schieppati, 2003). Proprioception may play a key role in anticipating these gravitational effects (Dalecki & Bock, 2013; Proske, 2005; Soechting, 1982; Soechting & Ross, 1984; Street, Wt, Lemay, & Bertram, 2004; Swinnen, Jardin, Meulenbroek, Dounskaia, & Van Den Brandt, 1997; C. J. Worringham & Stelmach, 1985; Charles J Worringham, Stelmach, & Martin, 1987). These studies suggest that proprioception may have different sensitivities to movement within the vertical plane which could be a function of movement in relation to a gravitational vector. The configuration of the arm may also play a large role in the sensitivity that can be achieved for specific movements and positions.

Modeling and simulation studies

Reaching and pointing tasks are very commonly used in research to compare contributions of vision, movement control, and position sense to movement errors (G. A. Apker et al., 2011; Berkinblit, Fookson, Smetanin, Adamovich, & Poizner, 1995; Blouin et al., 1993; Darling & Miller, 1993; Flanders, Tillery, & Soechting, 1992; Ghez et al., 1995; Goble & Brown, 2008; Gosselin-Kessiby, Kalaska, & Messier, 2009; McIntyre, Berthoz, & Lacquaniti, 1998; Sober & Sabes, 2003; Vindras & Viviani, 1998). Some studies have specifically examined the outcomes of eliminating visual feedback of reaching tasks (Gregory A Apker & Buneo, 2012; Gregory A Apker, Darling, & Buneo, 2010; Carrozzo et al., 1999; R. J. van Beers et al., 1998). A lot of information about differences between the roles of proprioceptive, visual, and motor function have been garnered by studies such as these. However, it is very difficult to complete dissociate these contributions in a reaching task where the individual components are so heavily intertwined. Any active reaching task is unable to eliminate the contribution of motor predictions produced by forward models from sensory components including proprioception. Some aspects can be isolated using modeling and simulation (Buneo, Boline, Soechting, & Poppele, 1995; Shi & Buneo, 2012; Robert J van Beers, Haggard, Wolpert, & Beers, 2004) but instrumented/robotic based assessment methods allow for passive movement of the limb which can provide experimental evidence to verify the veracity of simulation studies by eliminating motor factors as much as possible.

Proprioceptive Dysfunction

Pathophysiology

Proprioceptive deficits can be caused by a wide range of conditions that can affect the central nervous system (CNS) and peripheral nervous system (PNS) including, but not limited to, stroke, Parkinson's disease (PD), diabetes, traumatic brain injuries, some orthopedic injuries, and peripheral nerve or spinal injuries. For our purposes this discussion will be limited to large fiber sensory neuropathy and stroke survivors. These groups can suffer from proprioceptive deficits in position sense and kinesthesia as well as higher level disorders of body schema including neglect.

An extreme disorder where embodiment is not intact is called body integrity identity disorder, also called somatoparaphrenia, where a person feels that a part of their body, typically a hand or foot, does not belong to them and can lead to them seeking unnecessary amputations (Brugger & Lenggenhager, 2014). Asomatognosia is another similar disembodiment syndrome where a person doesn't recognize part of their body as themselves but the error can be temporarily corrected by presenting evidence that it is their own body (Feinberg, Venneri, Simone, Fan, & Northoff, 2010). Typically, embodiment is used to describe the sensation of something being part of your own body. A healthy person understands the boundaries of their own body and has a sense of ownership over their limbs and body which is heavily influenced by proprioceptive sensations.

There have been cases where people with specific types of neurodegenerative disorders have lost nearly all proprioceptive ability without losing muscle control or other sensations. Several cases of this type of loss have been documented in Ian Waterman (IW) who lost his sense of touch as well as proprioception from the neck down after a severe flu caused an autoimmune response that damaged those nerves but left his motor control intact and GL (patient name not disclosed) who also lost all of her proprioceptive function while maintaining muscle control (Lafargue, Paillard, Lamarre, & Sirigu, 2003; Rothwell et al., 1982; Yousif, Cole, Rothwell, & Diedrichsen, 2015). This however is a very rare occurrence and more typically a loss of proprioception is one of multiple symptoms caused by an underlying disease or condition. People who have these disorders are of great interest in research into proprioceptive function because of intact motor control. This allows for experimentation of contributions proprioception to tasks when compared to healthy participants that would otherwise not be possible. Studies have shown that with proprioceptive loss vision is able to provide information for corrections to reaching movements however when vision is removed inability to detect arm configuration leads to errors in reaching the get worse over time (Ghez et al., 1995; Gordon et al., 1995). A loss of proprioception in this way appears to result in many compensatory mechanisms taking over to make accommodations that allow for at least some functional control. These accommodations can reduce errors caused by missing proprioceptive information.

People who have suffered a stroke will often have reduced motor function and some may suffer from proprioceptive loss although these deficits are not always comorbid (Dukelow et al., 2012). With proprioceptive loss motor functions may be left intact and could be functional with vision being able to provide feedback on movements. It may also be the case that proprioception is left intact while motor function is lost. Differences in functionality can be tested to see what deficits are occurring that could be leading to a loss of ability to perform ADLs. Depending upon the sensation and/or motor function loss the type of rehabilitation used should be different to account for the specific deficits of the patient.

Proprioceptive Assessment

Typically, research into proprioceptive loss arising from central causes focuses on stroke patients. Understanding proprioceptive loss more fully could lead to better treatments leading to more complete recovery. According to the Center for Disease Control (CDC) approximately 795,000 people have a stroke each year and over half of stroke survivors have some form of reduced mobility (Benjamin et al., 2017). Approximately 60% of stroke survivors show at least some proprioceptive loss which is highly correlated with visuospatial neglect (Semrau, Wang, Herter, Scott, & Dukelow, 2015). Motor deficits and proprioceptive loss are largely independent after a stroke although proprioception plays a critical role in ADLs. The overall cost of care for people who have had a stroke is estimated at 34 billion per year in the United States and is the leading cause of serious long term disability (Benjamin et al., 2017).

Research directed at quantifying proprioceptive loss and treatments to aid in recovery of proprioceptive function could provide massive quality of life impacts for the hundreds of thousands of people that have a stroke every year. Understanding how this loss occurs and the best ways to help recovery is critical to helping people with this deficit lead the most normal life possible. Although current rehabilitation approaches do attempt to address the deficits arising from proprioceptive loss, these efforts are hampered by difficulties in accurately and reliably assessing proprioception. Difficulties with current clinical assessments of proprioception, as well as improved methods employing instrumented or robotic paradigms are discussed in detail below.

Clinical Neuro Exam

Typical proprioceptive assessment in a clinical setting can consist of something as simple as a thumb or big-toe localization test which consists of moving a toe and having the patient determine the direction of movement. An example of this assessment can be seen in Figure 4. This is a very coarse test used to quickly assess if there is a deficit as most people with typical functioning proprioception would have no problem correctly determining the direction of movement. However, this type of assessment is not easily repeatable making it difficult to measure small changes in proprioceptive sensitivity over time or with different rehabilitation programs. This type of assessment typically only classifies people as having intact proprioception, deficit proprioception, or lack of proprioception. Having only these course assessments of proprioception can be useful in a clinical setting to quickly determine if a problem exists for which more testing could be done. However, if researching the efficacy of different rehabilitation programs more precise data about sensitivity and how those may change over time is a necessity. When full recovery is not expected or possible then more thorough tests become necessary.

Standardized tests of sensorimotor function

Clinically, standardized tests of sensorimotor function are also used to indirectly assess proprioceptive function. For example, one commonly used test is the Fugl-Meyer (FM) which tests multiple dimensions of motor and sensory function, including proprioception, and gives an in-depth view of specific deficit types common in stroke

(Fugl-Meyer, Jääskö, Leyman, Olsson, & Steglind, 1975). The FM does take longer than some other more targeted assessments but gives a clearer picture of overall deficits that patients may have. With a more complete picture patients can get personalized sets of exercises to improve their specific deficits during rehabilitation. The FM test does take approximately 50-60 minutes to perform so other assessments such as the toe localization test are used to screen for gross deficits very quickly to determine if a more complete FM test would provide useful information.

Although the FM is the most commonly used assessment of motor and proprioceptive function in the clinic, especially for post-stroke assessment, there are other measures that can be used. Other tests are often used in specific circumstances that may not be possible with the FM. For example, walking tests, such as the six-minute walk test (6MWT) measures the distance a person can walk within 6 minutes but gives a much different measure of functioning than the FM. People doing the test must be mobile and able to safely walk at least some small amount and can measure functional mobility while the FM measures balance and motor function separately. The Berg Balance Scale (BBS) also focuses on assessing balance during standing and measures functional ambulation which gives more information about a patients risk to fall when moving or standing. Some tests are specifically designed to test patients with large or small deficits which may lead to a floor or ceiling effect on the result. Any low functioning test designed for people who have lost some motor function because of a stroke will not give robust information about proprioceptive differences in the typical population because the test incorporates activities that any neuro-typical individual should be able to easily accomplish. Specific assessments must be used in the right situation and for the studies presented in this dissertation clinical tests would have been ineffective because of the small differences being observed from a healthy population.

Robotic Assessment – 2d

Prior research has used 2d robotic setups to measure proprioception using many different tasks across many different populations (Adamo & Martin, 2009; Ghez et al., 1995; Goble & Brown, 2008; Gordon et al., 1995; Proske & Gandevia, 2012; Sainburg, Ghilardi, Poizner, & Ghez, 1995; R. J. van Beers et al., 1998; Wilson, Wong, & Gribble, 2010; Wrisberg & Winter, 1985). These tests are easily repeatable with a high reliability between experimenters and participants, helping to minimize any subjectivity in the assessments. Some studies use measurements of single joint movements, displacement detection, and many other proprioceptive tasks for assessment of the degree of proprioceptive loss. All these different approaches have their own pros and cons depending upon the specific aspect of proprioception being tested. Specifically, some of these tasks measure kinesthesia, sense of effort, or position sense and often focus on balance or other modalities where proprioception is important. This dissertation is primarily focused on upper limb position sense although other methodologies will be briefly discussed.

A commonly used research robot for upper limb movement and proprioception uses a 2d planar arm with a manipulandum (Dukelow et al., 2012, 2010; Kenzie, Semrau, Hill, Scott, & Dukelow, 2017; Simo et al., 2014; Wilson et al., 2010). They can be moved programmatically, be made compliant to the user's movement, apply different force environments or perturbations during movements, and easily connects to control a cursor on an attached screen to create "games" or tasks that are easily understood by participants. This allows for easy manipulation of vision during experiments to elucidate specific proprioceptive issues as well as visuomotor interactions during tasks.

Robotic Assessment – 3d

Some studies have assessed proprioceptive abilities in 3-dimensional (3d) space. An early assessment used one hand to set a location (criterion) and then the position had to be recreated with the same or opposite hand (Carson, Elliott, Goodman, & Dickinson, 1990). This was reproduced with and without having visual information available demonstrating that visual information and recreating the position with the same hand resulted in less error. Another measured active reaching to targets that had been presented either visually, passively by an experimenter moving their arm to the target, or with an active movement corrected by the experimenter to bring the finger to the target and then back to the starting position before having participant move to the target (Adamovich, Berkinblit, Fookson, & Poizner, 1998). This showed that active movements were the most accurately and precisely reproduced while passive motions resulted in the most variability. The effect on proprioception of having shoulder surgery has also been measured (Kasten et al., 2009). The most recent proprioception study quantified three-dimensional (3d) sensitivity of the wrist to rotational and angular changes for wrist flexion, extension, adduction, abduction, pronation, and supination (Marini et al., 2017). In 2D, differences in proprioception have been observed depending upon the location of the limb in the workspace and the direction of movement (Dukelow et al., 2012, 2010; Simo et al., 2014; Wilson et al., 2010). This begs the question if those results would extrapolate into a 3d space and show similar differences depending on the direction of movement. The first two sets of experiments in this dissertation are directly related to expanding upon those studies and developing a more complete picture of proprioception than prior ones.

Treatment and/or Management

Current physical and occupational therapy for stroke survivors typically focuses on motor rehabilitation. Motor deficits are common among stroke survivors and do have a major impact on ADLs. Proprioceptive deficits are fairly common, effecting 34-64% of stroke survivors (Connell, Lincoln, & Radford, 2008) however less focus is given to these deficits despite their also large contribution to ADLs. Motor recovery is not a specific topic being discussed here; focus will be on neuromodulation approaches that target proprioceptive deficits in order to improve rehabilitation practices in the future.

Peripheral Stimulation

Transcranial Direct Current Stimulation

Transcranial Direct Current Stimulation (TDCS) has been used in many different capacities and was an expansion of more invasive stimulation used to initially study muscle contractions that had previously been used in animal preparations (Parent, 2004). With such a long history of use, TDCS has been used to study or manipulate many different systems. Within a clinical setting these range from some of the earliest looking at major depression in a patient in 1801 (Parent, 2004), motor function (Santarnecchi et al., 2014), pain (Antal et al., 2008; Borckardt et al., 2012; Fregni, Gimenes, et al., 2006; Lefaucheur et al., 2017), PD (Benninger et al., 2010; Boggio et al., 2006; Fregni, Boggio, et al., 2006; Pereira et al., 2013), stroke (Baker, Rorden, & Fridriksson, 2010; Fregni et al., 2005; Jo et al., 2009; Schlaug, Renga, & Nair, 2008), multiple sclerosis (MS) (Cuypers et al., 2013; Ferrucci et al., 2014; Mori et al., 2013), schizophrenia (Brunelin et al., 2012; Göder et al., 2013; Smith et al., 2015; Vercammen et al., 2011), and many others. Although some studies have shown a lack of effect for treatment of some conditions so TDCS is not the panacea some have portrayed it to be (Volpato et al., 2013). A stimulation paradigm that is well known to the general public is electro-convulsive therapy (ECT) which has a terrible reputation but is still known to be very effective for intractable major depression. Less torturous options are available that have been shown to be effective include deep brain stimulation (DBS) which although does require a surgery could be argued is less invasive in terms of long term negative effects than ECT. Current research typically uses small amperage (1-2ma) to investigate effects of TDCS as well as probe the functions of stimulated structures. Small dosage TDCS is thought to be causing subthreshold alterations to resting potential depending on the current flow direction relative to the axons. Depending on the location and direction of current flow cortical circuits response can be enhanced or dampened (M. A. Nitsche & Paulus, 2001; Priori, Berardelli, Rona, Accornero, & Manfredi, 1998). This effect has been shown in motor cortex (Santarnecchi et al., 2014), somatosensory cortex (Matsunaga, Nitsche, Tsuji, & Rothwell, 2004), and visual cortex (Antal, Ambrus, & Chaieb, 2014). Although it is clear that this stimulation is reaching the brain and altering activity there is evidence that a large portion of the stimulation is not making it through the skull but is instead traveling through other tissues (Miranda, Lomarev, & Hallett, 2006; Underwood, 2016) and action potentials that are caused could be traveling outside of targeted brain structures to other neural circuits

(Overstreet, Klein, & Helms Tillery, 2013). Even with stimulation reaching the deep structures of the brain, as much as 90% of the current being applied is moving through surrounding tissue which may be causing stimulation on unintended targets such as cranial nerves that would also have downstream cognitive effects (Miranda et al., 2006; Underwood, 2016).

This technology has also been shown to have benefits to working memory, attention, and perception (Coffman, Clark, & Parasuraman, 2014). Some of these studies have focused on enhancing functional tasks as well as decreasing learning time for those tasks with TDCS and have been very promising (V. P. Clark et al., 2012). More studies are being done to determine the safety and effectiveness of this stimulation for people who don't need it for any type of medical intervention. However, some companies, such as foc.us, have even produced TDCS devices meant for neural enhancement for everyday life and not for any type of medical condition. These devices do have scientific backing for enhancing specific tasks but as with any consumer product the promises are often more than what has been rigorously tested scientifically. The use of these devices is very popular in biohacking and tech circles gaining attention with multiple articles being written about their use and effectiveness in the Guardian, Aeon, and Wired (Burkeman, 2014; Choi Mary HK, 2013; Christian, 2014). Thankfully these types of devices show little possibility of negative side effects for the general public even though stimulation could lead to long term changes which may or may not be beneficial (Davis & van Koningsbruggen, 2013).

TDCS shows great promise for clinical applications, enhancement, and as a tool to probe neural circuitry function. With its fairly simple design and ability to be used outside of clinical settings easily these types of stimulation paradigms have already found itself "in the wild" being used by biohackers and others for supposed neural enhancement and other off-label uses. With a large collection of people using this technology many new uses are being tested even if it's not being done in the most scientifically sound way. The problem is that this technology exists and any type of stimulation of neural structures could cause long lasting changes and could cause harm to people sensitive to those disturbances. TDCS is explained as non-invasive but any type of stimulation that could cause changes may not be as harmless as some people think (Davis & van Koningsbruggen, 2013). Although the safety of TDCS is fairly well supported, use by individuals unfamiliar with limitations and safety parameters could unintentionally do harm.

Transcutaneous Electrical Nerve Stimulation

Transcutaneous Electrical Nerve Stimulation (TENS) has been used to treat some types of pain in athletic, medical, and dental settings. TENS being a more generic term which includes trigeminal, vagus, or other nerve stimulation. A growing body of work is increasing our understanding of the effects TENS has on task learning, memory, attention, pain, cortical circuitry effects and more. There is some evidence showing that, depending on the nerve stimulated, TENS can alter functioning of the ascending reticular activating system (ARAS) which has modulatory effects on many other cortical circuits (Dijk, Scherder, Scheltens, & Sergeant, 2002). The ARAS is mostly related to the norandrenergic system which regulates activation of the sympathetic nervous system and has wide reaching effects on many other cortical circuits as well as some influence over some viscera function (Dijk et al., 2002). Many reports of benefits in Alzheimer's disease (Merrill et al., 2006; E.J.A. Scherder, Bouma, & Steen, 1995; Sjogren et al., 2002; Van Someren, Scherder, & Swaab, 1998), aging (Erik J.A Scherder, Van Someren, Bouma, & v.d. Berg, 2000), stroke (Karnath, 1995; Lin, Sun, Wang, & Xie, 2018; Robbins, Houghton, Woodbury, & Brown, 2006), and depression (Cook et al., 2013; Schrader, Cook, Miller, Maremont, & DeGiorgio, 2011) may all be related to a general activation of the ARAS and activation of the noradrenergic system (Sara, 2009).

Most of these prior experiments use different stimulation parameters which makes direct comparisons of any of the outcomes very difficult. Many studies using stimulation are open-label and participants are aware of the treatment they are receiving and no control group is included (Cook et al., 2013; Schrader et al., 2011; Trevizol et al., 2016). This is a good place to start and results are promising but for clinical use more studies using blinded controls are needed. The parameter space for TENS is very large and there doesn't appear to be a clear, linear progression of effects. Dose response curves may be altered by a change in any parameter making the feature space multi-dimensional which requires a lot more data to be collected to develop an understanding of expected outcomes. Parameterization by different labs seems to be idiosyncratic to what they found to be beneficial early on. Parameters include the amplitude, pulse duration, inter-pulse interval, ratio of biphasic pulses if balanced stimulation is being used, and frequency which can all be changed and appear to alter the types of fibers within the nerve that are stimulated causing different downstream cortical changes (Chase, Nakamura, Clemente, & Sterman, 1967; Ruffoli et al., 2011).

General effects of increased TENS dosage can lead to wildly different results because of not well understood mechanisms of action that lead to different cortical circuits being activated downstream. Some work has been done to elucidate specific fiber types activated by different stimulation but with such a large feature space much more work will need to be done to map possible outcomes based on the parameters used. Promising results for many different ailments make this a promising area of study and a more complete understanding of these effects could lead to many new treatments for refractory ailments.

Trigeminal Nerve Stimulation

Trigeminal Nerve Stimulation (TNS) has become a topic of interest recently with more studies examining its effects and similarities between vagus nerve stimulation (VNS – discussed below) as well as TDCS. Trigeminal stimulation is an excellent target for therapeutic stimulation because the supraorbital branch, as well as other branches, are easily targeted with stimulation above the eye and on the forehead. This is similar to vagus nerve stimulation that can target the auricular branch that enervates a portion of the ear. Small battery powered devices can be easily kept on the body to power electrodes because of the small amount of power needed for vagus or trigeminal stimulation devices. TNS has been investigated as a possible treatment for depression (Degiorgio, Fanselow, Schrader, & Cook, 2011), migraines (J Schoenen et al., 2013; Jean Schoenen et al., 2013), and epilepsy (Cook et al., 2013; Degiorgio et al., 2011; C. M. DeGiorgio, Murray, Markovic, & Whitehurst, 2009; Christopher M. DeGiorgio, Shewmon, Murray, & Whitehurst, 2006; Christopher M DeGiorgio et al., 2013; Schrader et al., 2011; Soss et al., 2015).

A lot of studies that have focused on TDCS may also have implications for TNS because in a cadaver study it was shown that most of the current applied that was thought to stimulate cortical tissue is instead passed through the outer layers of soft tissue and may lead to stimulation of other structures, specifically cranial and facial nerves (Dijk et al., 2002; Underwood, 2016). TNS may be able to produce more precise effects via stimulation of specific fiber types that TDCS may not be able to accomplish because of the constant stimulation applied. Nerve stimulation has been shown to be able to activate different subsets of nerve fibers that could lead to different downstream effects (Ruffoli et al., 2011). Although these studies have been done in the vagus nerve similar activation could also be achieved in the trigeminal nerve.

Vagus Nerve Stimulation

Vagus Nerve Stimulation (VNS), while sometimes more invasive requiring an implant around the vagus nerve but also transcutaneous stimulation, has been shown to be effective in reducing seizures (Fan, Hsu, Chang, Chen, & Tsai, 2018; Kulju, Haapasalo, Lehtimäki, Rainesalo, & Peltola, 2018), refractory migraines (Mauskop, 2005; Sadler, Purdy, & Rahey, 2002; Straube, Ellrich, Eren, Blum, & Ruscheweyh, 2015), cluster headaches (Gaul et al., 2016; Mauskop, 2005), heart failure (De Ferrari et al., 2011), Alzheimer's disease (Merrill et al., 2006; Sjogren et al., 2002), anxiety (George et al., 2008), depression (Nemeroff et al., 2006; Sackeim et al., 2001; Xiong et al., 2018), and obesity (Göbel, Tronnier, & Münte, 2017). Vagus cuff implants have risks of complications including infection, vocal cord paresis, and pharyngitis among others (Ben-Menachem, Revesz, Simon, & Silberstein, 2015). Many of these can be avoided by a skilled surgeon but reduced dependence upon implanted devices in favor of non-invasive stimulation is preferable to avoid many of these complications (Ben-Menachem et al., 2015). Even with non-invasive stimulation there are still effects on the nervous system that are not well known. Especially for long-term stimulation over multiple sessions over weeks or even years. The assumption that stimulation that doesn't require a surgical implant avoids any harmful effects could lead to unintended changes or damage to people participating in these studies even though we do our best to reduce those risks (Davis & van Koningsbruggen, 2013).

Non-invasive vagus nerve stimulation has become more common and has been shown to be viable for many of the same treatments as the implanted stimulator devices. Some of these devices stimulate the auricular branch of the vagus nerve and has been shown to help with otherwise intractable depression (Paulino Trevizol et al., 2015; Trevizol et al., 2016) and epilepsy which was otherwise resistant to more standard treatments (Fan et al., 2018; Kulju et al., 2018) as well as cognition enhancements (Steenbergen et al., 2015). The move to stimulation which doesn't require an implant can make the treatment more attractive to try without the risks of surgery or going through a procedure for a device that doesn't improve outcomes for everyone. While many people see reduced symptoms and are helped by VNS others discontinue use or even report an increase in seizures with VNS devices (Ben-Menachem et al., 2015). By using non-invasive stimulation, the effects can be observed to see if the treatment is beneficial for the individual and use can be easily discontinued without the need for an explant surgery. Many of these stimulator devices have become quite small and easy to use. Some targeting the auricular branch of the vagus nerve look like an earphone and they fit inside the ear comfortably without using single use disposable electrodes or complicated electronics that would need a technician to set up.

These devices are shrinking and making it easier for patients to easily follow care plans at home. Overall non-invasive VNS is becoming more common and research being done into the specific benefits and disorders that can be treated with such devices is expanding. Approvals for common usage of these in clinics as well as at home requires more information about useful parameters, safety, and efficacy.

Stochastic Resonance

Stochastic Resonance (SR) has been used to enhance detection of sensorimotor functions but most typically has been used to enhance postural control during balance tasks. Applying a low level of noise via vibrotactile motors or electrical stimulation can improve detectability of balance signals in multiple clinical populations as well as normal functioning adults (Costa et al., 2007a, 2007b; Dettmer, Pourmoghaddam, Lee, & Layne, 2015; Hijmans, Geertzen, Zijlstra, Hof, & Postema, 2008; Mulavara et al., 2011; A. A. Priplata, Niemi, Harry, Lipsitz, & Collins, 2003; A. Priplata et al., 2002; Ross, 2007). This simple addition of noise to a sensory system can lead to enhancement of specific function if the noise level is set appropriately. Other groups have shown the specific effects of differing levels of noise on specific mechanoreceptors that would be responsible for the perceptual enhancement seen in other studies using SR (Ivey, Apkarian, & Chialvo, 1998). Specifically, a noise stimulus that is too small will have little to no effect because it isn’t having enough of an effect on the targeted signal. Also, a noise signal that is too strong can overwhelm the targeted signal and remove any information the subject might be able to gain. Different studies accommodate for this fact in different ways but many use the subject’s own threshold of detection as the starting point for stimulation amplitude

(Hijmans et al., 2008) while others use standardized levels of stimulation with a repeated measures design (Ross, 2007). In systems that befit from small amounts of noise there is a goldilocks zone for stimulation where it enhances the endogenous signal just enough to make it reliability detectable without overpowering it.

This technique can enhance the detection of signals and make them functionally useful however application of noise can reduce the precision in those signals. In most cases where this would be useful the precision is not as important as making the signal detectable, so it is at all useful instead of being below threshold for the individual. There is even evidence showing that these types of SR effects can be seen cross-modally leading to enhancement of one sensory modality when noise is provided for another (E. Lugo, Doti, & Faubert, 2008; J. E. Lugo, Doti, & Faubert, 2012). This effect is theorized to be caused by increased activation of sensory integration neurons that facilitate the enhancement of one sensory signal because of the noise being added via a different modality.

Stochastic resonance has been shown to be useful in many different biological systems from vision (Simonotto et al., 1997), touch (Ivey et al., 1998; Moss, Ward, & Sannita, 2004), balance (Dettmer et al., 2015; Hijmans et al., 2008; Mulavara et al., 2011; A. A. Priplata et al., 2003; A. Priplata et al., 2002; Ross, 2007), hearing (Morse & Evans, 1996; Zeng, Fu, & Morse, 2000), and is likely commonly present in endogenous systems (Moss et al., 2004). SR has been fairly well investigated in several different domains as a non-invasive paradigm that can lead to enhanced detectability of sub-threshold signals leading to increased efficiency of the entire system (Moss et al., 2004).

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is used to probe deeper structures of the brain with much higher precision that previously discussed techniques in this chapter. While others can provide specific stimulation, they are typically limited to nerves available with transcutaneous techniques. TMS allows for penetration of a very focal stimulation location through the skull. TDCS can provide general stimulation to large portions of the brain and can go very deep into the brain but it is not well targeted. TMS can target specific cortical structures by using a pre-existing structural MRI scan of the subject and subjective detection or motor outputs to locate regions of interest in individuals. The stimulation can penetrate through some layers of cortical tissue but does have a limited depth that it can target that prevents it from being used to probe deep brain structures such as the hippocampus or limbic system directly. By being able to isolate very small cortical structures very small areas of the brain can be probed for specific contributions in processing.

Several different techniques for TMS exist that provide different outcomes for the targeted area. Online stimulation can directly disrupt activity during a task and has very little long term effect on outcomes while repetitive TMS (rTMS) including theta burst stimulation (TBS) can cause effects that last from minutes to days after stimulation ceases (Oberman, Edwards, Eldaief, & Pascual-Leone, 2011). This type of stimulation is the most promising for clinical effects or enhancement because of the long-lasting effects.

Many TMS studies have also looked the effects on depression with promising results for people who have depression that isn’t helped with medication. With variations of stimulation type there have been many promising results (Chung, Hoy, & Fitzgerald, 2015; Yip et al., 2017). Although not all people had reduced symptoms after the stimulation the majority that did show that this is a treatment that would be worth trying if other treatments aren't effective. With TMS being a non-invasive treatment that does not require surgery this is something that could be easily incorporated into other treatments such as counseling and medications.

TMS has also been looked at as a treatment for Parkinson's disease and many studies have shown that there is improvement of some aspects of PD with application of TMS (Moisello et al., 2015; Xue-fei ZHAO et al., 2015). Common targets for these studies include motor cortex, prefrontal cortex, and parietal cortex.

Phosphenes can also be induced via TMS stimulation of the occipital lobe, specifically the visual cortex, and have been used to isolate components of the visual system that would be difficult to study without using TMS as a tool. Many studies have used phosphenes to bypass sections of visual processing to help elucidate the specific transformations occurring in different cortical circuits important for visual processing (Knight, Mazzi, Beck, & Savazzi, 2015; Rangelov, Müller, & Taylor, 2015)

Direct, focused stimulation or inhibition of neural circuitry is another great tool to be used for clinical research as well as basic research to understand the underlying cortical circuits of the brain.

Ultrasound Stimulation

Ultrasound (US) has more recently been shown to be able to modulate neural activity. Previously US has been used for medical imaging and is used in small offices by technicians daily. The use of US for stimulation is newer than other types of stimulation discussed before this, but it does show a lot of promise. With US stimulation, sometimes called focused ultrasound (FUS), a very small focal area can be stimulated in deep structures of the brain. While the specific cause of these effects is still not completely known the ability of US to effect cortical circuits is not in question (Fini & Tyler, 2017; W. Lee et al., 2016; Legon et al., 2014; Mueller, Legon, Opitz, Sato, & Tyler, 2014; Tyler, Lani, & Hwang, 2018). As with all stimulation technologies stimulation itself could have negative consequences (Davis & van Koningsbruggen, 2013) however some of the first uses of US for cortical alterations was showing that they could be used to produce lesions without the need to reach the location surgically or with an instrument in order to ablate it (Fry, Mosberg, Barnard, & Fry, 1954). Current US methods to induce cortical alterations use a much smaller amplitude signal to produce cortical changes which makes the much safer to use in human subjects.

This technology, although newer than other stimulation techniques, can produce more focused stimulation in deep structures of the brain which gives researchers a better tool to use to probe neural circuits more precisely. TMS can stimulation shallow structures with small focal points while US can do the same but also target deep structures. TDCS has been shown to be effective at enhancing specific responses and helping with some medical conditions but it effects very large areas of cortex. US provides a great ability to target specific structures that previously hasn’t been possible.

Enhancement vs Rehabilitation

All the technologies that allow for peripheral stimulation of the nervous system can be used in multiple different ways. One such distinction that should be clear is that between enhancement and rehabilitation. Removing peripheral stimulation from the discussion this is the difference between helping a person recover motor strength after an accident or stroke and someone without any type of deficit going to the gym to increase their strength by lifting weights. Both people may be lifting weights, but the end goals are different even if that line may occasionally be blurred.

Rehabilitation practices aim to restore function back to levels before some negative event or at least recover them to a level where they are useful. Typically, the amount of recovery is dependent upon what is possible for that person as well as what their goals are. Rehabilitation must be done for everyone to help them as much as possible given the situation as well as what their goals are. Some people may not want or need to be able to run a mile while others want to go back to running marathons. Each person is unique, and the specific treatments will reflect that. There are many studies that have shown the effects of stimulation on different disorders which do show very promising results for rehabilitation as can be seen in specific sections under the peripheral stimulation heading in this chapter.

Enhancement has garnered much more attention in the recent past and will probably continue to grow. There are countless articles discussing the possibilities of peripheral stimulation to enhance specific tasks. Most of these technologies are adapted from other uses and are not formally studied as often as the rehabilitative uses are. Many people have taken it upon themselves to look at these technologies and use them in non-prescribed and non-studied ways. These people are often referred to as bio-hackers and get a lot of attention for some of their more public uses of enhancement technology. There is evidence that there may be benefits but nearly all the people using the technology are not doing it in a controlled, scientific way so most of their claims are dubious. A lot more controlled work needs to be done looking at these technologies, how they are being used, and what the actual effect is on performance.

Using this technology for rehabilitation seems to have very little downside while enhancement can lead to discussions about a technological divide between people who can afford the technology and those that can't as well as many other debates about the eventual outcomes and uses of the technology and what that will mean for societies in the future. This dissertation will not be discussing those ideas in depth as they have been covered in multiple other formats.

Signal Detection Theory

Signal Detection Theory (SDT) has been commonly used in electrical engineering, specifically for sensor quantification, as well as psychology, and economics. SDT is a more complete way of looking at data where a decision was forced between the detection of a signal or not. Some people use percent correct when looking at this type of data but that fails to capture some of the important aspects of decision making, especially when a system has unequal numbers of times when a signal is present versus not. If only percent correct is looked at with an unbalanced number of trials for each then bias can play a significant role in skewing the data. Instead of percent correct for these studies we used SDT measures of d', which is the discriminability of a signal, and c, or bias, values which considers the strategy of the detector or, in the case of human research, the person making the decision. A diagrammatic view of basic SDT principles can be seen in Figure 5. Using SDT techniques it's necessary to collect hit rates (pH) and false alarm rates (pF) which are used to calculate d'. To find d' the z score transformation of the pF is subtracted from the z score of pH.

$$d' = z(pH) - z(pF)$$

Bias is another measure within SDT that was used. It can be calculated as the half of the z transform of the hit rate added to the z score of the false alarm rate.

$$c = -(z(pH) + z\,(pF))/2$$

This essentially measures the likelihood of a response being the same which would be shown as positive values or different which would result in positive values as the output. By viewing both values together the discriminability of the signal can be determined, and an understanding of the limits and capabilities of whatever underlying detection method can be tested. Other measures can be found within the same framework of SDT however, the studies presented in this dissertation focus on D' and c. In the case of this dissertation it is testing the functional limits of position proprioception while being able to effectively disregard some of the underlying mechanisms that have differing contributions. These functional outcomes are important in clinical settings where those are the end goal of therapies. Different strategies can be employed to alter the rates of misses and false alarms depending upon the severity of outcomes for those events. If it's extremely critical that a specific form of cancer be found during a screening, then the test may be able to tolerate more false positives because the test could be administered multiple times to ensure accuracy. All these considerations can be explored with signal detection theory to identify what types of sensitivity and bias are best for a given situation. The experiments in this dissertation don’t allow us to alter the discriminability of the signals and alter those parameters but instead seek to more fully quantify the inherit differences found within typical functioning proprioceptive systems.

Aims of Research

The first aim of the current research discussed in this dissertation is to quantify proprioceptive position sense in 3d space. Prior studies have used tests limited to the 2d plane (tabletop) but have thoroughly classified many aspects of proprioception within those constraints. These studies were meant to add to the body of knowledge about the ability and limitations of proprioception. The first two studies specifically measuring proprioception on three-dimensional space that had previously been unexplored and testing the effect of arm posture on sensitivity. These studies specifically studied position sense of proprioception based on the design of the experiment. Designing the paradigm based on the need to make assessment possible for any arbitrary angle and arm posture lead to the use of the 2AFC task forcing a choice between same or different position as previously presented. This new paradigm was used to test six different directions (up, down, left, right, forward, and backward) from a set starting location. Adducted and abducted arm postures were also tested to compare differences in sensitivity between left, right, forward, and backward. Predicted outcomes were that anisotropic effects would be present based on previous research but that depending upon direction and arm configuration differences in proprioceptive sensitivity may be altered from previously published data.

The second portion of this dissertation was related to TENS and its ability to alter functional outcomes of proprioceptive function. The original intent was to explore the ability of trigeminal nerve stimulation to affect function proprioceptive outcomes however testing of multiple peripheral locations lead to a broader understanding of the impacts of cranial nerve stimulation in general.

CHAPTER 2 MATERIALS AND METHODS

Introduction

Many studies of proprioceptive sensitivity have been conducted but have typically been limited in to movements in a 2-dimensional plane or single joint movements. Constraining the movements to 2 dimensions for research is convenient and eliminates unnecessary complexity from the experiment allowing for faster iteration around questions that don't require the 3-dimensional capabilities. However, body motion is rarely ever constrained to 2 dimensions during natural use. For this reason, prior to this research, very few studies have measured proprioception within a 3d workspace. Among these are a study where proprioception was assessed before and after shoulder surgery to determine the amount of proprioceptive loss and the other was focused on finding differences in proprioception based on the way the presentation modality of targets (Adamovich et al., 1998; Kasten et al., 2009). Expanding current proprioceptive assessment into 3d space is a necessary next step in gaining a fuller understanding of the proprioceptive system that hasn't been done before.

As there was not already a well-established paradigm for this type of assessment creation of a new protocol was a primary focus. Previous studies had used techniques that could be easily adapted for the new paradigm. The main difference in this task is using a 2AFC (same-different) task that allowed for simplification of subject instructions. This chapter will outline the final general experimental paradigm, rational behind design decisions compared to early protocols, and data analysis methods used.

Experimental Apparatus

Robotic Assessment

A 7-DoF anthropomorphic robot arm (LWR4+, KUKA Inc.) was used for the robotic assessment. Typical participant configuration is shown in Figure 6. This robot has a maximum payload of 7 kg, a maximum reach of 1178 mm (when completely stretched), a maximum joint speed of 110-204º/sec (joint dependent) and a repeatability of +/- 0.05 mm. The robot can be controlled in zero-impedance, i.e. completely compliant to user's motion, and is able to measure arm motion and human-robot interaction forces at a frequency of 1kHz. Subjects interacted with the robot while seated in a chair that could be locked in place and adjusted in height for comfort and easy placement of subject relative to the robot. The subject's arm was coupled to the robot through an arm trough which was secured to the arm with a Velcro strap which also stabilized and controlled the forearm and wrist joint. In experiment 1 the elbow of the subject was left in an adducted posture next to the body. Experiment 2 altered the arm position to be abducted by using a custom-made sling attached to the ceiling. Excessive motion of the shoulder girdle and trunk were restricted by means of waist and shoulder straps that were attached to the chair. Earmuffs with audio input and microphones were worn by the subjects. By playing white noise and the passive noise cancelling of the ear muffs all outside distractions and noise from the robot were eliminated. The earmuffs were also used to present beeps as auditory cues during trials. An emergency stop button was provided for subjects that could be pressed to immediately stop all movement of the robot as a safety precaution. Subjects were also required to close their eyes during experiment to eliminate any visual feedback of their arm so that the test relied on only their proprioception. Early versions of the experiment included blindfolding the participant but issues of drowsiness and the ability to easily take breaks became an issue which simply having people close their eyes easily remedied.

Software Control

This section will describe the various components that interact to allow for control of the robot, participant interaction, and stimulation control.

The experiments were controlled via a Linux-based desktop computer running custom C programs for control of the Kuka robotic arm as well as for control of the participant cues and data collection. These programs were created by Bryan Whitsell and adapted by Josh Klein to allow for control of the stimulation in a way that ensure that the correct number of trials were performed for each stimulation location and distance. The program that controls the core operation of the robot, using custom trajectory files, and communicating with subroutine programs is the Robot & Experiment Control executable. The reason for breaking these programs out into separate executable files that use shared memory for communication. The purpose of having multiple programs to handle each component instead of a single program is because of a safety feature of the Kuka robot that causes it to lock itself in place if communication from the controlling computer is ever interrupted. By allowing the main program to continue executing while other programs handled tasks that would typically cause a delay prevented the robot from locking which would have made the experiment impossible to run. This also allowed for the subsidiary programs to be simpler and easier to understand if edits did need to be made in the future.

The main control program would also produce signals for the cue program to send auditory cues to the participant. This process was simplified as it was a one-way communication. This is similar to the way that the user input program functioned. At the end of a trial the main program would write the shared memory location to a value and wait for it to be changed by the user input program indicating that a user response (same or different) had been entered. During this time, it could maintain communication with the Kuka robot to ensure that the security measures weren't inadvertently activated causing the robot to lock and requiring everything to be restarted in order to resume the experiment. A block diagram of the software used for the experiment can be seen below in Figure 10.

Experimental Protocol

Participants were brought into the lab for the experiment which was approved by the Arizona State University Institutional Review Board and all participants gave written informed consent in accordance with the Declaration of Helsinki. Participants were briefed on the experimental procedures and expectations for interacting with the robot and were aware that their position sense was being tested but were naïve to the specific purpose of the study. Participants would then have the task explained in more detail before being seated in a chair in front of the robot. The plane of robot motion was aligned with a parasagittal plane passing the shoulder joint. The reference location was then established by moving the subject to approximately 5˚ azimuth and 0˚ elevation relative to the estimated (average) center of rotation of the shoulder joint and at a distance from the shoulder that corresponded to ~80% of the subject's total arm length. This position was comfortable for most participants with little to no shoulder fatigue over the course of the experiment. During data collection participants were required to keep their eyes closed.

Experiment 1 tested the arm in an adducted posture where the elbow was positioned comfortable at the side of the torso. In Exp. 2, data were collected for an additional abducted arm posture where the subject's elbow was held nearly level with the shoulder and reference location by a sling hung from the ceiling. In experiment 3 the adducted arm posture was again used. An example of these postures can be seen in Figure 7.

Task Paradigm

A fixed one alternative forced (same/different) choice (1AFC) task was used for all experiments presented in this dissertation. A 1AFC task is simply a "go"/"no go" response, in this case "same" or "different", that is required after the presentation of the two stimuli. Fixed in this context means that the reference location was not varied between trials but was held constant throughout the experiment. Common in the literature is the use of a 2AFC task which typically requires a judgment of direction of change as opposed to a 1AFC task which only requires detecting if a change has occurred. A 1AFC task is typically used when it may be difficult for subjects to learn the basis for discrimination as the responses are simplified no matter the direction of the movement or the posture of the arm. This apparatus could test along any arbitrary axis and the design needed to allow for those arbitrary paths to be tested in possibly future experiments. For this reason, these experiments used a 1AFC task that could be extended to those arbitrary angles and different arm postures which may not have been as easily described by subjects during the experiment.

Stimuli (reference and test positions) were presented successively which allows for all movements to be completed within the right arm. This design does introduce a memory component into the task by having subjects compare a currently felt position to a remembered position. Although, previous studies have shown that performance on tasks with a memory component is similar to tasks that do not require memory of the location such as position matching, posture matching, or reaching to marked locations (Wilson et al., 2010).

During the instruction's participants were told they should verbally respond "same" if the judgment position was the same as the test position or "different" if it was not. Before beginning data collection trials, the subjects performed 3-5 practice trials to ensure they understood the task and any misunderstandings were corrected at this point and the experiment only continued if they appeared to understand the task. If after 15 trials a subject still exhibited difficulty in understanding the task the subject was excused from the experiment and no further testing was conducted. If the subject had been performing the task but then informed the experimenters that they had been doing the task incorrectly the subject was also excused from the experiment and no further testing was conducted.

Experiment 1 included testing six different directions (up, down, left, right, forward, and backward) at 4 distances (1, 2, 3, and 4cm) from the reference location. Experiment 2 using the abducted arm posture tested at the same distances but only for left, right, forward, and backward directions from the reference. This was limited to only these four directions because movements up/down in combination with the sling could have caused uncomfortable or painful positions of the participants' arm. Experiment 3 tested all four distances as well but only in the down direction while the stimulation location and frequency were varied.

Single Trial Description

A single trial consisted of the subject's arm being held at the starting position for 2 seconds before a movement to a distractor position would begin. The robot stopped at the distractor position for 250ms before moving back to either the same starting location or a different position. Two beeps through headphones would cue the subject to respond if the location was the "same" or "different" verbally. After the response the robot would move out to another distractor location, stop briefly again, and return to the starting position where a single beep would be played to the subject to indicate they were back at the reference location again. A diagram of an example trial can be seen in Figure 8and the layout of the block design can be seen in Figure 9.

Movement parameters

The distractor position movements were meant to reduce cues that would have been provided by a direct movement of the robot from the reference location to the judgement position for that trial. These movements between points used curved paths with a radius of curvature that was randomized between 2.44 cm and 15.8 cm (mean: 9.52). A constant velocity was used and the total movement time was fixed to .5 seconds. These constraints caused velocities to range from 1.2 cm/s to 7.8 cm/s (mean: 3.7 cm/s). The total time between leaving the reference position and arriving at any subsequent judgment position was also fixed at 3.75s including the movement time as well as the short delay at the distractor position.

In experiment 1 and 2 a single distance in one direction included 30 trials (15 same and 15 different). Each direction was tested using four equally spaced distances of 1cm, 2cm, 3cm, and 4cm from the reference location. In pilot testing of the paradigm there was little to no increase in sensitivity between 4 and 5cm distance so the experiment was limited to a maximum distance of 4cm. This helped keep the experiment within a two hour experimental window to avoid subject fatigue.

Block Design

On 'same' trials, the first and second stimuli were always the test position, while on 'different' trials, the first stimulus was always the test position and the second was one of the other judgment positions. Same and different trials were randomly selected but balanced over the course of the entire block. Testing four distances within a direction and two directions for each subject resulted in 240 total trials total which took about 1-1.5 hours to complete. Paperwork, explanation of the task, and example trials took approximately 15-20 minutes resulting in approximately 2 hours in the lab for each participant.

At the start of each block a set of criterion movements were performed to give information about the distance between the reference position and the 'different' position for that set of 30 trials. These movements allowed the participants to establish a criterion value between the same and different points that is used to make the judgement about if the position required for this task. These criterion movements consisted of three direct movements from the reference position to the 'different' position, a short delay, and then a direct return to the reference location. These movements were important to ensure they knew the magnitude of difference from the reference to the test position. If these movements weren't included then the transition from a 4cm to a 1cm block could have resulted in their criterion value not being updated correctly. These movements ensured that the participant was aware of this position difference being tested leading to a more accurate assessment of proprioceptive ability.

Every 15 trials subjects were asked to take a short rest (5-60 seconds) to view their arm while moving and/or stretching it. This helped to minimize the possibility of proprioceptive drift as well as to reduce any fatigue or strain the subject was experiencing during the experiment (Wilson et al., 2010). After every rest participants replaced their hand on the trough of the robot and were asked to isometrically contract and relax their arm to reduced the possibility of thixitropy (Proske & Gandevia, 2012). The layout of this block experimental design can be seen below in Figure 10.

During experiment 3 the extra step of placing electrodes at the appropriate locations was added. More detail on this will be discussed in Chapter 4.

Data Analysis

Subjects' responses were analyzed in MATLAB (The Mathworks Inc.). The proportion of trials where subjects responded "different" when the stimuli were different (*pH*), aka probability hit or "hit rate", and the proportion of trials where the subjects responded "different" when the stimuli were the same (*pF*), aka probability false or "false alarm rate", were used to calculate *d'*, a measure of sensitivity derived from signal detection theory (Kingdom & Prins, 2016). This measure is preferred over percent correct (*Pc*) in most situations, as the latter can be greatly influenced by bias (i.e. a subject's tendency toward "same" or "different" responses). *d'* was calculated as:

$$d' = z(pH) - z(pF) \qquad (1)$$

where *z()* denotes a z-score transformation. For comparison we also report *Pc*, defined as:

$$Pc = [pH+(1-pF)]/2 \quad (2)$$

Additionally, bias (c) was calculated for stimulation experiments to view any possible alterations to response bias. Positive values denote a conservative bias where participants more often responded “same” or, more generally, that a signal was not present. Negative values denote a liberal bias where “different” or, generally, that a signal was there. A conservative bias typically corresponds to a smaller hit rate and small false alarm rate while liberal bias corresponds to a high hit rate as well as an elevated false alarm rate. Bias (c) is calculated as:

$$c = -.5 * (z(pH)+z(pF))$$

D’ calculated in MATLAB was used for all statistical analyses that were completed using SPSS.

D’ was calculated for each distance and direction in both Exps. 1 and 2. For Exp. 1, differences in d’ as a function of displacement distance and direction were assessed using a two-factor mixed ANOVA (within subjects factor: distance; between subjects factor: direction). Multiple comparisons were conducted using Tukey’s HSD procedure. Outliers were removed before statistical analysis by using the median absolute deviation (MAD) procedure with a scaling factor (b) of 3 (Leys, Ley, Klein, Bernard, & Licata, 2013).

Experiment 2 was designed to investigate the effects of arm posture on sensitivity. Analyses focused on displacement distances that showed the most variation across directions in Exp. 1 (i.e. 2 and 3 cm). For each distance, independent t-tests were used to compare sensitivity between arm postures for a given axis (forward/backward; leftward/rightward), as well as to compare sensitivity between axes for a given arm posture. We also combined data for the leftward-rightward directions and forward-backward directions to facilitate comparison with previous results (Wilson et al., 2010).

Experiment 3 was looking at the effects of transcutaneous electrical nerve stimulation on sensitivity (d') and bias (c) of the worst performing direction from experiment 1 to show possible enhancement of proprioceptive function if it was present. Analysis was done similarly to experiment one using a 4 x 3 x 2 mixed ANOVA (within subjects factors: distance (1, 2, 3, and 4cm) and stimulation location (forehead, neck, and shoulder), between subjects factor: stimulation frequency (30hz and 300hz)).

CHAPTER 3 ANISOTROPIC PERCEPTION OF LIMB ENDPOINT POSITION IN THREE-DIMENSIONAL SPACE

Abstract

Proprioception refers to the senses of body position, movement, force and effort. Previous studies have demonstrated workspace and direction-dependent differences in arm proprioceptive sensitivity within the horizontal plane. In addition, studies of reaching in the vertical plane have shown that proprioception plays a key role in anticipating arm configuration dependent effects of gravity. This suggests that proprioceptive sensitivity could vary with the direction of arm displacement relative to the gravitational vector, as well as with arm configuration. To test these hypotheses, and to characterize proprioception more generally, we assessed the direction-dependence and arm postural-dependence of proprioceptive sensitivity in 3D space using a novel robotic paradigm.

A subject's right arm was coupled to a 7 DOF robot through a trough that stabilized the wrist and forearm, allowing for changes in configuration largely at the elbow and shoulder. Sensitivity was evaluated using a "same-different" task, where the subject's hand was moved 1-4 cm away from an initial "test" position to a 2nd "judgment" position. The proportion of trials where subjects responded "different" when the positions were different ("hit rate"), and where they responded "different" when the positions were the same, ("false alarm rate"), were used to calculate d', a measure of sensitivity derived from signal detection theory. Initially, a single initial arm posture was used and displacements were performed in six directions: upward, downward, forward, backward, leftward and

rightward of the test position. In a follow-up experiment, data were obtained for four directions and two initial arm postures.

As expected, sensitivity (d') increased monotonically with distance for all six directions. Sensitivity also varied between directions, particularly at position differences of 2 and 3 cm. Overall, sensitivity reached near maximal values in this task at 2 cm for the leftward/rightward directions, 3 cm for upward/forward and 4 cm for the downward/backward directions. In addition, when data were grouped together for opposing directions, sensitivity showed a dependence upon arm posture. These data suggest arm proprioceptive sensitivity is both anisotropic in 3D space and configuration-dependent, which has important implications for sensorimotor control of the arm and human-robot interactions.

Introduction

Proprioception refers to the senses of body position ('position sense'), movement ('kinethesis') and force/effort/heaviness (Proske & Gandevia, 2012). Loss or impairment of proprioception is a natural sequela of a host of conditions affecting both the central nervous system (CNS) and peripheral nervous system (PNS) including stroke, traumatic brain injury, Parkinson's disease, diabetes and even certain orthopedic injuries. Loss of this 'sixth sense' impairs perception of the relative configurations of body parts in space ("body schema") and dramatically affects the planning and control of limb and body movement (Ghez et al., 1995; Gordon et al., 1995). This in turn has profoundly negative effects on the performance of essential activities of daily living, leading to reduced quality of life.

Despite its importance for normal sensorimotor functioning, proprioception remains enigmatic and its assessment in the clinic remains relatively crude. Robotic technologies have recently been employed in an attempt to improve the fidelity of clinical assessments of proprioception. For example, Scott and colleagues have developed a version of the classic position matching paradigm that employs the use of planar robotic exoskeletal arms (Dukelow et al., 2010). In this paradigm, one exoskeletal arm passively moves the test arm into a test position and the subject then attempts to actively match this position with the other arm. Analysis focuses on quantifying differences between the positions generated by the passively and actively moved arms. In experiments comparing the proprioceptive abilities of stroke survivors with age-matched controls, this method was found to have good interrater reliability and revealed that approximately one half of examined patients exhibited some degree of proprioceptive (position sensing) impairment (Dukelow et al., 2010).

Other investigators have combined the use a planar robotic manipulandum with sensory psychophysical techniques to assess proprioception. For example, one recent study compared proprioceptive function between a group of neurologically intact human subjects and a group of stroke survivors (Simo et al., 2014). Proprioception was probed using both an arm movement detection and a hand force detection task. Subject performance was quantified using two parameters: detection threshold, which is the minimum magnitude of displacement or forces that can be reliably detected, and choice uncertainty, the variability in responses about the detection threshold. These measures were able to distinguish between subjects with and without proprioceptive deficits and were found to be relatively reliable in repeated tests separated by a period of one week.

Robotic devices have also been used to aid in understanding the proprioceptive abilities of neurologically intact subjects (Cressman & Henriques, 2011; Dukelow et al., 2012, 2010; Fuentes & Bastian, 2010; Simo et al., 2014; Wilson et al., 2010). Most of these studies have focused on proprioceptive abilities within a single horizontal plane and have demonstrated (among other findings) that proprioceptive sensitivity depends on both the position of the arm and the direction of arm displacement within the 2D workspace. Although wrist proprioception has recently been characterized in 3D (Marini, Squeri, Morasso, Konczak, & Masia, 2016), similar tests for the proximal arm have yet to be conducted. However, recent studies have shown that arm kinematics vary for movements performed along different directions in the vertical plane (i.e. with and against the direction of the gravity vector) in a manner that is consistent with an optimization of both inertial and gravitational forces (Berret et al., 2008; Gentili et al., 2007; Le Seac'h & McIntyre, 2007; Papaxanthis et al., 2003). Moreover, other work suggests that anticipating such gravitational effects on the arm depends strongly on input from the proprioceptive system (Dalecki & Bock, 2013; Proske, 2005; Soechting, 1982; Soechting & Ross, 1984; Street et al., 2004; Swinnen et al., 1997; C. J. Worringham & Stelmach, 1985; Charles J Worringham et al., 1987). This raises the possibility that proprioceptive abilities could also differ for movements performed along different directions in the vertical plane, more specifically as a function of direction with respect to the gravitational vector. By a similar logic, proprioceptive sensitivity could vary with changes in arm configuration.

Although previous work suggests that arm proprioceptive sensitivity could vary with direction and configuration in 3D space, a formal test of this hypothesis has yet to be conducted. Here we used a 7 degree of freedom robotic arm, a 1 AFC ('same-different') psychophysical paradigm and analysis techniques derived from signal detection theory (SDT) to perform such a test. In an initial experiment, sensitivity to differences in arm position was quantified and compared for arm displacements along six directions in 3D space: leftward, rightward, forward, backward, upward and downward with respect to a fixed reference position. In a 2nd experiment, sensitivity was compared for four directions (leftward/rightward, forward/backward) and two initial arm postures (adducted and abducted). Preliminary results of these experiments have previously been reported in abstract form (Josh Klein, Whitsell, Artemiadis, & Buneo, 2015, 2016, 2017).

Materials and Methods

Participants

The experimental protocol was approved by the Arizona State University Institutional Review Board and all subjects gave written informed consent in accordance with the Declaration of Helsinki. Subjects were briefed on the experimental procedures and expectations for interacting with the robot and were aware that their position sense was being tested but were naïve to the specific purpose of the study. In an initial experiment (Exp. 1) examining the effects of displacement direction on proprioceptive sensitivity, seventy-eight (78) subjects (49 female, 29 male) were tested for two of the six displacement directions in a given session. Two subjects (one male, one female) were determined to be outliers in both tested directions based on their median absolute deviation and were removed from further analysis. After outlier removal, the total number of subjects analyzed in each direction was as follows: Upward: 30; Downward: 27; Backward: 19; Forward: 15; Leftward: 18; Rightward: 17. In a follow-up experiment (Exp. 2) examining the additional effects of arm posture, 20 subjects (8 female, 12 male) were tested in two of four directions (Backward, Forward, Leftward, Rightward) in an abducted arm posture. One female subject was determined to be an outlier for both tested directions as was removed from further analysis.

Apparatus

A 7-DoF anthropomorphic robot arm (LWR4+, KUKA Inc.) was used for the robotic assessment (Fig. 1). This robot has a maximum payload of 7 kg, a maximum reach of 1178 mm (when completely stretched), a maximum joint speed of 110-204º/sec (joint dependent) and a repeatability of +/- 0.05 mm. The robot can be controlled in zero-impedance, i.e. completely compliant to user's motion, and is able to measure arm motion and human-robot interaction forces at a frequency of 1kHz. Subjects interacted with the robot while seated in a chair that could be locked in place and adjusted in height for participant comfort. Human arms were coupled to the robot through an arm trough which was secured to the arm with a Velcro strap and which also stabilized and controlled the forearm and wrist. Excessive motion of the shoulder girdle and trunk were restricted by means of waist and shoulder straps that were attached to the chair. In addition, subjects were given a switch which could be pressed at any time to immediately stop motion of the robot.

In Exp. 1, a single "adducted" arm posture was employed. During an initial calibration procedure, the plane of robot motion was first aligned with a parasagittal plane passing the shoulder joint. The initial test position of the hand-robot coupling was then specified, which was located at approximately 5˚ azimuth and 0˚ elevation relative to the estimated (average) center of rotation of the shoulder joint and at a distance from the shoulder that corresponded to ~80% of the subject's total arm length. In Exp. 2, data were collected for an additional "abducted" arm posture. This was achieved by rotating the upper arm about an axis connecting the shoulder to the hand and suspending the arm with a sling attached by ropes to the ceiling of the testing room. In this way the upper arm and forearm were contained in an approximately horizontal plane as shown in Fig. 2.

Experimental Procedures

Experimental Design

Sensitivity to differences in limb position were evaluated using a fixed "AX" or "same-different" task (also referred to as a 1 alternative forced choice (AFC) same-different task) (DeCarlo, 2013; Kingdom & Prins, 2010; Macmillan & Creelman, 2005; Micheyl, Kaernbach, & Demany, 2008). This is a discrimination paradigm involving the successive presentation of a pair of stimuli, with half the trials containing stimuli pairs that are the same and half the trials containing pairs that are different. Subjects are required to determine whether the pair presented in a given trial is the 'same' or 'different' (Kingdom & Prins, 2010). The modifier 'fixed' refers to the fact that in this experiment the second stimulus was compared relative to a fixed, standard stimulus (the 'test position'), which differs from 'roving' designs where both stimuli are varied along a continuum. The same-different task requires the detection of a change but not the identification of the direction of this change (Micheyl et al., 2008) and is preferred over the more standard 2 AFC task in situations where subjects would have difficulty learning the basis for discriminating stimulus pairs (Kingdom & Prins, 2010). This would very likely be the case for discriminating positions/directions along arbitrary, oblique axes in 3D space.

As shown in Fig. 3, our stimuli consisted of “judgment” positions that were located at different distances from the test position along a given direction. The spacing and orientation of the judgment positions could be easily manipulated in software, allowing for the testing of proprioception along any arbitrary direction/axis in 3D space. For a given movement direction, four judgment positions were used, which were spaced 1 cm apart in one of the six directions. As noted above, on a given trial, the two stimuli pairs could be the same or different. On ‘same’ trials, the first and second stimuli were always the test position, while on different trials, the first stimulus was always the test position and the second was one of the other judgment positions. As illustrated in Fig. 4, each ‘different’ stimulus was tested in a separate block, and the order of these blocks differed for different directions. For a given block of same-different trials, 30 trials were conducted (15 same and 15 different). These trials were performed in blocks of 15, separated by a short (~ 20 second) rest period. Within each 15 trial block, the same and different positions were randomized on a trial-by-trial basis. During the intervening rest periods, subjects were encouraged to view their arm, in order to minimize the possibility of proprioceptive drift (Wilson et al., 2010).

Experimental Protocol

Prior to performance of experimental trials, subjects performed 3-5 practice trials to ensure that they understood the task. Before each block of 30 trials subjects first experienced the robot moving their arm from the test position into the judgment position for that block in order to familiarize them with the testing environment and to ensure their comfort during the experiment. These “criterion” movements also provided subjects with information about the expected difference between positions in the given block. Subjects were instructed that on a given trial the robot would move their arm on a random path that would end either at the test position or the judgment position. Subjects were told that they should respond ‘same’ if the judgment position was the same as the test position or ‘different’ if it was not. If after 15 trials a subject still exhibited difficulty in understanding the task the subject was excused from the experiment and no further testing was conducted. If the subject had been performing the task but then informed the experimenters that they had been doing the task incorrectly the subject was also excused from the experiment and no further testing was conducted.

During blocks of experimental trials, subjects were instructed to remain as relaxed as possible and to avoid resisting or assisting motion of the robot. To minimize the possibility of muscular thixotropy on position sense (Proske & Gandevia, 2012), subjects were told to isometrically contract their arm muscles at the start of the experiment and before continuing after experimental breaks. This also served to reduce any fatigue or strain the subject was experiencing during the experiment. Figure 9 illustrates the sequence of events on a single trial. At the beginning of the trial the robot brought the arm to the test position and a single auditory tone was delivered. After a delay of 2 s the robot then moved the arm away from the test position to a random via point (maximum distance from the test position: 10 cm; minimum distance: 2 cm). After stopping very briefly (250 ms) at the via point, the robot then moved the arm either back to the test position ('same' trials) or to the judgment position ('different' trials) for that block. This was followed by the presentation of two auditory tones indicating the end of the trial. The subject was then required to respond 'same' or 'different', indicating that the judgment position corresponded to either the original (test) position or the judgment position.

Movements to and from the via points were used to minimize the possibility that movement-related cues could be used to infer hand position (Wilson et al., 2010). These movements involved paths with a radius of curvature that was randomized between 2.44 cm and 15.8 cm (mean: 9.52). A linear velocity profile was used and the total movement time was fixed. As a result, peak velocities ranged from 1.2 cm/s to 7.8 cm/s (mean: 3.7 cm/s). As a result of these constraints, the total time between leaving the test position and arriving at any subsequent judgment position was also fixed at 3.75 s.

Data Analysis

Subjects' responses were analyzed in MATLAB (The Mathworks Inc.). The proportion of trials where subjects responded "different" when the stimuli were different (pH), aka "hit rate", and the proportion of trials where the subjects responded "different" when the stimuli were the same (pF), aka "false alarm rate", were used to calculate d', a measure of sensitivity derived from signal detection theory (Kingdom & Prins, 2010). This measure is preferred over % correct (Pc) in most situations, as the latter can be greatly influenced by bias (i.e. a subject's tendency toward "same" or 'different' responses). d' was calculated as:

$$d' = z(pH)-z(pF) \qquad (1)$$

where z() denotes a z-score transformation. For comparison we also report Pc, defined as:

$$Pc = [pH+(1-pF)]/2 \qquad (2)$$

D' was calculated for each distance and direction in both Exps. 1 and 2. In Exp. 2 we also combined data for the leftward-rightward directions and forward-backward directions to facilitate comparison with previous results (Wilson et al., 2010).

Statistical analyses on population data

All statistical analyses were conducted in SPSS 25. For Exp. 1, differences in d' as a function of displacement distance and direction were assessed using a two-factor mixed ANOVA (within subjects factor: distance; between subjects factor: direction). Multiple comparisons were conducted using Tukey's HSD procedure.

Experiment 2 was designed to investigate the effects of arm posture on sensitivity. Analyses focused on displacement distances that showed the most variation across directions in Exp. 1 (i.e. 2 and 3 cm). For each distance, independent t-tests were used to compare sensitivity between arm postures for a given axis (forward/backward; leftward/rightward), as well as to compare sensitivity between axes for a given arm posture.

Results

Effects of displacement distance and direction

As expected, proprioceptive sensitivity increased monotonically with distance from the test position. Figure 11 shows plots of % correct (A), hit rates/false alarm rates (B), and d’ (C) as a function of distance from the starting (“test”) position. Data for the upward and downward directions are shown for a single subject. The plots for % correct show that for this subject, performance improved with distance and for the downward direction this increase was fairly linear. However, for the upward direction, trends with distance were somewhat different. Here, performance did not differ appreciably from 1-2 cm but improved rapidly from 2-3 cm. As a result of these differing trends, performance exceeded 75% correct (a standard threshold for discrimination) at 3cm for the upward direction and 4 cm for the downward direction. Regardless of these differences, the overall trends with distance reflect the simple fact that discriminating between positions is more difficult when these positions are closer together than when they are spaced farther apart.

The plots for d’ and hit rate/false alarm rate highlight additional subtleties in this subject’s performance. Similar to % correct, d’ increased monotonically with distance for both directions. However, for d’ sensitivity at 2 cm differed somewhat between directions though no such differences were apparent for % correct. Differences between d’ and % correct can be understood from the hit rates and false alarm rates which are used to calculate d’. Even though the hit rate for the upward direction was greater than the hit rate for the downward direction at 2 cm, this subject also produced more false alarms for the upward direction. In other words, a bias towards ‘different’ responses contributed strongly to the increased number of hits, rather than simply an increased ability to discriminate the positions effectively. As a result, sensitivity (as defined by d') was actually somewhat larger for the downward direction. This shows that at the single subject level, d' provides additional insights into discrimination than % correct alone can provide. As a result, analyses of sensitivity at the population level were focused exclusively on d'.

Effects of distance and direction were also evident at the population level. Figure 12 shows hit rates/false alarm rates and sensitivity (d') as a function of distance for all directions. Data for opposing directions are shown separately in different rows. As was observed at the single subject level, d' generally increased with distance for the upward/downward directions (Fig. 7B). Greater sensitivity can be observed for the upward direction at 3 cm, with this difference appearing to arise from higher hit rates and somewhat lower false alarm rates for the upward direction. For the forward/backward directions (Fig. 7D), sensitivity also increased with distance. Here differences between directions were more consistent, with sensitivity for the forward direction appearing greater than for the backward direction at all distances up to 3 cm. Again, those differences appeared to be due both to higher hit rates and lower false alarm rates, in this case for the forward direction. For the leftward/rightward directions (Fig. 7F), sensitivity only differed markedly at 2cm, with rightward being greater than leftward. Here, the greater sensitivity did not appear to arise at all from higher hit rates, instead the observed differences were due almost entirely to substantially lower false alarm rates in the rightward direction.

Although Fig. 7 suggests that sensitivity was sometimes similar between opposing directions, isotropy was not a general finding. A two-factor ANOVA using data from all distances and directions revealed significant main effects of both factors on sensitivity (Distance: $F(3, 360) = 348.04$, $p<.001$; Direction: $F(5, 120) = 6.36$, $p<.001$), as well as a significant interaction effect ($F(15, 360) = 2.60$, $p<.01$). Such trends are clearly discernible in Fig. 8. First, these boxplots illustrate that d' values generally increased with distance for all directions. For example, for the downward direction mean d' values for 1-4 cm were 0.4, 1.31, 1.55, and 2.27 respectively. Although d' varied with distance for the other directions as well, trends with distance were not identical across directions. At 1 cm, d' values were relatively low in magnitude and virtually identical for all directions while at 4 cm d' was consistently larger but also comparable across directions. In contrast, clear differences in sensitivity across directions are apparent at the middle distances (2 and 3 cm). As a result, trends with distance were direction-dependent, as suggested by the ANOVA. To better illustrate this, we computed an estimate of the maximum sensitivity in this task by taking the global median across all directions at 4 cm (gray horizontal line). For the leftward and rightward directions, sensitivity approached this estimate of maximum sensitivity at a difference in position of 2 cm. This same level of performance was not reached until 3 cm for the upward and forward directions and not until 4 cm for the downward and backward directions. This is largely consistent with the post-hoc Tukey tests, which showed that sensitivity for the downward (Mean = 1.29, SD = 0.98) and backward (Mean = 1.26, SD = 1.12) directions differed significantly from both the leftward (Mean = 1.83, SD = 0.94) and rightward (Mean = 2.05, SD = 0.95) directions (downward vs leftward: $p < .01$; backward vs leftward: $p < .01$; downward vs rightward: $p < .001$;

backward vs rightward: $p < .001$). Thus in this study the manner in which proprioceptive sensitivity improved with distance was anisotropic.

Effects of arm configuration

Previous studies of arm proprioception in the horizontal plane have also reported direction-dependent differences in sensitivity. In particular, Wilson et al. (2010) demonstrated that proprioceptive acuity was greater for positions along a forward-backward axis than along a leftward-rightward axis. In contrast, in the present study, near maximal sensitivity was achieved at 2 cm for the leftward and rightward directions, with other directions (including forward and backward) reaching similar levels of performance only at 3 or 4 cm. This implies that in the present study, proprioceptive sensitivity was more acute for leftward/rightward directions than other directions, in apparent contradiction to the findings of Wilson and colleagues. However, an important methodological difference existed between these two studies. In Wilson et al. the arm was contained within the same horizontal plane in which hand position was varied. In the present study the shoulder was adducted; therefore the arm was rotated almost 90 out of the horizontal plane. To assess whether the apparent discrepancy between the two studies was due to the use of different initial arm configurations we conducted a follow-up experiment that assessed proprioceptive sensitivity along four directions using both adducted and abducted postures.

Varying initial arm posture resulted in changes in proprioceptive sensitivity. We first compared sensitivity between opposing directions for each arm posture. As in Exp. 1, no significant differences were found between the leftward and rightward directions or between the forward and backward directions for either arm posture. Therefore, to facilitate comparison with Wilson et al. (2010) data for opposing directions were grouped together for analysis. Figure 14 shows the mean (+/- SD) of the d' values for each posture, grouped for the leftward/rightward and forward/backward directions. As expected given the results of Exp. 1, in the adducted posture sensitivity at 2 cm differed significantly between the leftward/rightward (Mean = 1.93, SD = 0.83) and forward/backward axes (Mean = 1.12, SD = 0.61; t-test, $t(75) = 4.86$, $p<.001$). At 3 cm, sensitivity also differed significantly between axes in this posture (leftward/rightward Mean = 2.26, SD = 0.62; forward/backward Mean = 1.86, SD = 0.99; $t(79) = 2.20$. $p<.05$). However, in the abducted posture no differences between axes were found ($p=.07$ and $p=.4$ for 2 and 3 cm, respectively). At least at 3 cm this lack of difference appeared to be due largely to a significant decrease in leftward/rightward sensitivity between adducted (Mean = 2.26, SD = 0.62) and abducted (Mean = 1.81, SD = 0.57) postures (t-test, $t(58) = 2.64$, $p<.05$). In contrast, no statistically significant differences were found between postures for the forward/backward axis.

Discussion

Several previous studies have characterized the proprioceptive abilities of human subjects within a horizontal plane. Among other findings, these studies have demonstrated that proprioceptive sensitivity varies with the direction of arm displacement as well as the position of the limb within the horizontal plane. Here we employed a 7-DoF robot arm and analysis techniques derived from signal detection theory to characterize proprioceptive abilities along several axes in 3D space, including opposing directions parallel to the gravity vector (i.e. upward and downward), which have not previously been characterized. Although our task involved comparing a currently felt position with a remembered one, previous studies have shown that performance on such tasks is similar to tasks without a substantial memory period (Wilson et al., 2010). Overall we found that sensitivity depended on the distance between discriminated positions and, in agreement with previous findings, was also direction-dependent. The sensitivity profile for the upward direction was found to be similar to that of the forward direction and the profile for downward was similar to backward, with the latter two directions being the least sensitive overall at distances of 2-3 cm. In addition, when data were grouped together for opposing directions, sensitivity showed a dependence upon arm posture. These results suggest that arm proprioceptive sensitivity is both anisotropic and configuration-dependent in 3D space.

Relevance to clinical and laboratory assessment of proprioception

Despite the importance of proprioception for normal perceptual and sensorimotor functioning, proprioception remains incompletely understood and its assessment in the clinic is primitive and limited in scope. One major factor contributing to the enigmatic nature of this “6th sense” is that there is no universally accepted method for assessing proprioception. In the clinic, assessment is performed in a relatively coarse manner and typically addresses only position sense. In one method, a patient’s joint (typically one of the digits of the foot or hand) is alternately moved in two opposing directions and the patient is asked to discriminate between these positions (e.g. “up or ‘down?”). A second commonly used method involves position matching, where the arm to be tested (‘test arm”) is passively moved into a test position and the subject is then asked to actively reproduce that position with either the same arm (after moving the arm back to its starting position) or with the contralateral arm. Although these tests can be quickly administered and are easy for patients to understand they are also suffer from several disadvantages. For example, such tests provide only coarse, discrete measures of proprioceptive abilities, i.e. proprioception is typically classified only as impaired or absent (Simo et al., 2014). Such tests are also currently thought to be associated with poor (or at least questionable) inter-rater (Lincoln et al., 1991) and/or intra-rater reliability (Carey, 1995; Dukelow et al., 2010; Lincoln et al., 1991; Simo et al., 2014). In addition, since these tests require physically guiding a subject through the required movement, proprioceptive estimates obtained this way can be contaminated by tactile, force and movement cues conveyed by the examiner (Simo et al., 2014). For these and other reasons, such methods are of limited usefulness in assessing proprioception outside of the clinical setting and were not employed in the present study.

Errors in reaching and pointing have been used in the laboratory to infer the contribution of proprioception to position sensing and movement control in both neurologically intact subjects (G. A. Apker et al., 2011; Berkinblit et al., 1995; Darling & Miller, 1993; Flanders et al., 1992; Goble & Brown, 2008; McIntyre et al., 1998; Sober & Sabes, 2003; Vindras & Viviani, 1998) and patients (Blouin et al., 1993; Ghez et al., 1995; Gordon et al., 1995; Gosselin-Kessiby et al., 2009; Messier, Adamovich, Berkinblit, Tunik, & Poizner, 2003). Particularly relevant are studies involving movements without visual feedback of the moving hand (Gregory A Apker & Buneo, 2012; Gregory A Apker et al., 2010; Carrozzo et al., 1999; R. J. van Beers et al., 1998). Although these and other studies have provided a wealth of information about the relative roles of proprioception and vision in arm movement control, the active nature of reaching/pointing paradigms precludes isolation of the sensing aspect of proprioception from motor predictions derived from efference copy and an internal (forward) model. Although the contributions of sensory and motor processes can be partially disentangled using modeling and simulation techniques (Buneo et al., 1995; Shi & Buneo, 2012; Robert J van Beers et al., 2004), instrumented/robotic based assessment methods, which employ passive driving of the limb, can largely rule out the contribution of motor factors to proprioceptive function.

In the present study an instrumented (robotic) paradigm was used to quantify proprioceptive abilities. Early attempts at instrumented assessment typically allowed testing at only a single joint and still required the subject to actively move their limb or required the examiner to manually place the limb in position (Carey, 1995; Goble & Brown, 2008; H.-M. Lee, Liau, Cheng, Tan, & Shih, 2003; Street & Wt, 2008). As a result of these limitations, several groups have recently employed the use of multijointed robots in proprioceptive assessment (Cressman & Henriques, 2011; Dukelow et al., 2010; Erickson & Karduna, 2011; Fuentes & Bastian, 2010; Simo et al., 2014; Wilson et al., 2010). Robotic assessment has several advantages over traditional manual assessments and other instrumented tests. Typically several joints can be assessed at once and can be done so relatively quickly (Dukelow et al., 2010). In addition, the limb does not have to be manipulated by the examiner which, as previously noted, can often provide subtle movement related cues to the subject. Second, the high spatial precision of modern robots means that errors in repeated positioning of the limb are nearly non-existent relative to manual positioning. Lastly, the ratio-level nature of the data that can be acquired using robots means that assessment can be more quantitative and more likely to reveal impairment (Dukelow et al., 2010; Simo et al., 2014). Thus, using a high precision device such as a robot can greatly improve the objectivity and reliability of proprioceptive assessments.

One potential limitation of the approach used here was that subjects' arms were passively driven between positions. Since proprioceptors are most often stimulated during active movements, the extent to which our measurements provide a complete picture of proprioceptive abilities is unclear. However, recent work by Henriques and colleagues (2011) suggests that passive assessments may generalize well to at least some active contexts. These investigators assessed changes in perceived hand position after subjects either a) actively moved the handle of a manipulandum along a constrained linear path or b) had the handle passively moved along the same linear path (Cressman & Henriques, 2011). In both paradigms, once the hand reached the final position, subjects were required to make a two-alternative forced-choice (2 AFC) judgment about the position of their hand relative to a visual reference marker. Following adaptation to altered visual feedback of the hand, proprioceptive estimates were found to be biased in the same direction as corresponding reaching movements, regardless of the nature of hand displacement (i.e. active or passive). This suggests that passive driving of the limb, as employed in the present study, may provide a robust estimate of proprioceptive abilities under a variety of contexts (i.e. active and/or placement displacement of the limb).

Anisotropies in position estimation

Several previous studies have reported directional and workspace dependencies in proprioceptive abilities within the horizontal plane. For example, van beers and colleagues studied the ability of human subjects to localize visual or proprioceptive targets at three positions in the horizontal plane (R. J. van Beers et al., 1998). They found that subjects were more precise when localizing positions along an anterior-posterior axis than along an azimuthal one. In addition, subjects were more precise when localizing positions closer to the body than farther away. Subsequent work employing visuomotor adaptation paradigms (Robert J. van Beers, Sittig, & Gon, 1999; Robert J van Beers, Wolpert, & Haggard, 2002) confirmed the direction-dependent precision of both proprioceptive and visual localization and described some of the basic rules underlying the integration of information derived from these senses. The findings for proprioception were largely confirmed by a study involving direct examination of proprioceptive abilities employing a planar robot (Wilson et al., 2010). Here, subjects were required to judge the position of their hand with respect to either a remembered proprioceptive reference position or a visual reference. Judgment positions were attained via passive movements of the robots end effector (handle), which was grasped by the subjects. Proprioceptive acuity (i.e. sensitivity to change in hand position) was found to be greater for hand positions closer to the body and for changes in hand position occurring along an anterior-posterior axis. In addition these investigators found limb-dependent differences in proprioceptive bias (perceived location of the hand) and also found that bias was reduced when the hand was closer to the body than farther away.

In previous studies, workspace and directional differences in proprioceptive abilities were explained by geometric factors. For example, identical changes in hand position performed at different locations in the workspace would be expected to result in different relative changes in joint angle, i.e. smaller changes in joint angle for positions further from the body and larger changes closer in (Wilson et al., 2010). As a result, muscle spindles would stretch to differing degrees at these locations, giving rise to the observed differences in proprioceptive abilities. A similar mechanism is thought to underlie directional differences in proprioceptive abilities. Although a geometric argument makes sense, in 2D experiments changes in limb geometry and changes in the position of the hand in the work space are naturally confounded. Thus, it’s unclear if the differences observed in 2D are entirely geometric in origin or if they arise in part from other factors, such as the frequency distribution of workspace positions naturally visited by the hand (Slijper, Richter, Over, Smeets, & Frens, 2009) or asymmetries in the distribution of preferred sensory directions of arm muscle spindles (Bergenheim, Roll, & Ribot-Ciscar, 2000; Roll, Bergenheim, & Ribot-Ciscar, 2000). In the present experiments however, hand position and arm configuration were not confounded. This lends support to the idea that geometric changes, including those that don’t alter the position of the hand in the workspace, are an important factor in determining arm proprioceptive sensitivity.

Regarding performance for directions outside the horizontal plane, neurophysiological studies have reported that fewer neurons in the rat dorsal spinocerebellar tract (Bosco & Poppele, 2001; Valle, Casabona, Bosco, & Perciavalle, 2007) and primate somatosensory cortex (Tillery, Soechting, & Ebner, 1996) are tuned to movements/positions along the vertical axis than along other axes. This suggests that proprioceptive abilities should be diminished for arm displacements with substantial vertical components, a finding that was not generally observed here. That is, although sensitivity for the downward direction was poor relative to most other directions at intermediate distances, sensitivity for the upward direction was similar to the forward, leftward and rightward directions. The reasons for this discrepancy with neurophysiological studies are not immediately apparent. It should be noted however that some differences between the upward and downward directions were observed in this study. As mentioned previously, several studies have demonstrated robust differences in movement kinematics for upward vs downward arm movements (Berret et al., 2008; Gentili et al., 2007; Le Seac'h & McIntyre, 2007; Papaxanthis et al., 2003). Other work suggests these differences reflect the contribution of an internal model that is used in part to anticipate and exploit the anisotropic effects of gravity on the limb (Gaveau, Berret, Angelaki, & Papaxanthis, 2016). This model, presumably acquired during development, would depend in part on the perceived effort associated with moving in different directions in the vertical plane, information which the proprioceptive system is ideally suited to provide (Proske & Gandevia, 2012). Thus, in addition to the aforementioned factors, anisotropic perception of limb position in 3D space could partially reflect the influence of an internal model that incorporates the perceived effort associated with moving in different directions relative to the gravitational vertical.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

C.A.B. and J.K. conceived the experiments; C.A.B., J.K., B.W. and P.A.K. designed the experiments; C.A.B., J.K., and B.W. performed experiments; C.A.B. and J.K. analyzed data; C.A.B., J.K., B.W. and P.A.K. interpreted results of experiments; C.A.B. and J.K. prepared figures; C.A.B. and J.K. drafted manuscript; C.A.B., J.K., B.W. and P.A.K. edited and revised manuscript; C.A.B., J.K., B.W. and P.A.K. approved final version of manuscript.

CHAPTER 4 EFFECT OF TENS ON PROPRIOCEPTION SENSITIVITY

Introduction

Proprioception loss affects 60% of stroke survivors leading to problems performing activities of daily living (ADLs) which significantly reduces their independence and mobility (Benjamin et al., 2017; Semrau et al., 2015). The estimated cost of care for people who have had a stroke in the United States is $34 billion per year and is the leading cause of serious, long term disability (Benjamin et al., 2017). Proprioceptive dysfunction and loss can be caused by other disorders besides stroke, including, multiple sclerosis, spinal cord injuries, and diabetic neuropathy so the number of affected individuals is much higher than just those who have suffered a stroke. Therapies used in physical or occupational therapy can help ameliorate these deficits and help someone regain their independence and ability to perform ADLs. Neuromodulatory devices have shown to be extremely effective in some cases at altering neural functioning in very beneficial ways. For example, Deep brain stimulation (DBS), although extremely invasive and requiring neuro-surgery, is extremely effective at treating symptoms of Parkinson’s disease and major depression (R. J. Anderson et al., 2012; Limousin et al., 1995). The experiment presented here measures the effect of neuromodulation in the form of transcutaneous electrical nerve stimulation (TENS) via external electrodes on the forehead, neck, and shoulder. Prior evidence suggests that it may be possible to alter cognition, and by extension proprioceptive function.

Stimulation techniques and clinical applications

Effects seen with invasive technologies, such as DBS, have led to studies on the use of peripheral stimulation to treat disorders, which is much less invasive. Some peripheral stimulation methods such as transcranial direct current stimulation (TDCS), transcutaneous electrical never stimulation (TENS), trigeminal nerve stimulation (TNS), vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS), and ultrasound stimulation (US) have been investigated for their ability to help with depression, motor dysfunction, pain, Parkinson's disease, stroke, multiple sclerosis, schizophrenia, Alzheimer's, migraines, epilepsy, seizures, anxiety, obesity, and even heart failure (Antal et al., 2008; Baker et al., 2010; Benninger et al., 2010; Boggio et al., 2006; Borckardt et al., 2012; Brunelin et al., 2012; Cook et al., 2013; Cuypers et al., 2013; De Ferrari et al., 2011; Degiorgio et al., 2011; C. M. DeGiorgio et al., 2009; Christopher M. DeGiorgio et al., 2006; Christopher M DeGiorgio et al., 2013; Fan et al., 2018; Ferrucci et al., 2014; Fini & Tyler, 2017; Fregni et al., 2005; Fregni, Boggio, et al., 2006; Fregni, Gimenes, et al., 2006; Gaul et al., 2016; George et al., 2008; Göbel et al., 2017; Göder et al., 2013; Jo et al., 2009; Karnath, 1995; Kulju et al., 2018; W. Lee et al., 2016; Lefaucheur et al., 2017; Legon et al., 2014; Lin et al., 2018; Mauskop, 2005; Merrill et al., 2006; Moisello et al., 2015; Mori et al., 2013; Mueller et al., 2014; Nemeroff et al., 2006; Parent, 2004; Paulino Trevizol et al., 2015; Pereira et al., 2013; Robbins et al., 2006; Sackeim et al., 2001; Sadler et al., 2002; Santarnecchi et al., 2014; E.J.A. Scherder et al., 1995; Schlaug et al., 2008; J Schoenen et al., 2013; Jean Schoenen et al., 2013; Schrader et al., 2011; Sjogren et al., 2002; Smith et al., 2015; Soss et al., 2015; Trevizol et al., 2016; Tyler et al., 2018; Van Someren et al., 1998; Vercammen et al., 2011; Xiong et al., 2018; Xue-fei ZHAO et al., 2015). The ability to alter quickly alter neurological functioning to see if an individual does have clinical benefits without the need for surgery would give physicians more tools to improve people's lives. A more thorough breakdown of these technologies and their efficacy for specific diseases can be found in Chapter 1.

Currently neurological disorders are most often treated with medications which can be very effective but also often produce side effects. More recently deep brain stimulation (DBS) has been very effective at treating Parkinson's disease, epilepsy, and even depression. DBS is another tool that can be used when medications aren't effective however it is very invasive, requiring neurosurgery. In contrast to these other treatments trigeminal and vagus nerve stimulation can modulate activity in the same areas without invasive neurosurgery or side-effects from off target effects. TNS provides another way to modulate the activity in these cortical structures that would likely have therapeutic effects. Other treatments that alter basal ganglia function are effective treatments and another tool that could modulate those same structures is very likely to provide another modality for delivering those effective treatments. Being able to produce even a subset of the beneficial effects in a controlled, reliable way, using TNS without the need for surgery or drugs would be an amazing new tool for clinicians.

Stimulation for enhancement

While some studies have investigated the use of TENS in altering proprioceptive function in the context of improving balance and postural stability in neurologically involved populations, no studies have looked at using TENS for enhancement of proprioceptive sensitivity within a typical population (Chang et al., 2013; Jung, In, & Cho, 2017; Junhyuck, Dongkwon, Wonjae, & Seugwon, 2014; Shirazi, Shafaee, & Abbasi, 2014; Tyson, Sadeghi-Demneh, & Nester, 2013). These studies also provided TENS directly to peripheral, somatic nerves in regions of the body affected by the deficit including the bottom of the foot (through a conductive sock) (Tyson et al., 2013), the gastrocnemius (Chang et al., 2013; Junhyuck et al., 2014), medial quadriceps (Junhyuck et al., 2014), peroneal nerve (Jung et al., 2017), and the lower back from L1-L5 (Shirazi et al., 2014). More recently attention has turned toward exogenous, non-invasive stimulation with the goal of modulating cortical arousal systems to promote cortical neuroplasticity (V. P. Clark et al., 2012; Coffman et al., 2014; Kilgard, Rennaker, Alexander, & Dawson, 2018; Trumbo et al., 2016). Using these methods to enhance proprioception has not previously been investigated.

A different type of stimulation, transcranial direct current stimulation (TDCS), has been studied more heavily for enhancement. TDCS has shown to have benefits for working memory, attention, and perception (Coffman et al., 2014), increasing verbal fluency (Pisoni et al., 2018), and even accelerating the learning of complex tasks (V. P. Clark et al., 2012). Safety for use as an enhancement is very important because the interventions are not weighed against the negative impacts of allowing disease progression without treatment. TDCS as a technology appears to be safe, with very few documented side effects (Poreisz, Boros, Antal, & Paulus, 2007). It is clear from these studies that TDCS is producing results and causing some changes in cortical functioning. However, there is evidence that a large portion of the current being provided is staying in soft tissue around the head or traveling to other, unintended, targets and is not penetrating through the skull, as previously thought (Miranda et al., 2006; Underwood, 2016). TDCS and other types of stimulation may be having a similar effect because current may also be traveling to superficial branches of cranial nerves. This suggests that direct targeting of these cranial nerves such as TNS or VNS could produce many of the same enhancement effects that have been shown with TDCS. TENS is specifically meant to target these nerves so it could be possible to see many of the same enhancement effects that have been shown with TDCS in experimental designs that use TENS, including trigeminal nerve stimulation (TNS) or vagal nerve stimulation (VNS).

Proprioceptive Research

Many studies have attempted to quantify proprioceptive function in stroke patients and in un-affected populations (Adamo & Martin, 2009; Ghez et al., 1995; Goble & Brown, 2008; Gordon et al., 1995; Proske & Gandevia, 2012; Sainburg et al., 1995; R. J. van Beers et al., 1998; Wilson et al., 2010; Wrisberg & Winter, 1985). However, those studies did not test along a vertical axis and were limited to 2-dimensional testing. Recently, we developed a paradigm that allows testing of upper arm proprioception along arbitrary axes in 3d space and with different arm postures (Joshua Klein, Whitsell, Artemiadis, & Buneo, 2018). In that study it was shown that discrimination was least sensitive between points located along a downward direction from a reference location. As a result, in the present study downward movements were chosen to measure the effect of TENS.

Few studies have tested the effectiveness of TENS applied to cranial nerves for enhancement of cognitive or sensory functioning. Most previous studies targeted peripheral somatic nerves with the goals of enhancing balance, proprioception, or gait (Chang et al., 2013; Jung et al., 2017; Junhyuck et al., 2014; Shirazi et al., 2014; Tyson et al., 2013) Here we used a commercially available to stimulator (Digitimer, DS8R) to deliver current at 30hz and 300hz to peripheral branches of the trigeminal nerve, with the goal of influencing upper limb proprioceptive sensitivity.

Any observed enhancement could have implications for rehabilitation of upper extremity function following stroke and other disorders as well as for enhancing training or performance of tasks that demand high levels of proprioceptive sensitivity.

Methods

This experiment was conducted in the same way as Experiment 1 from Chapter 2 and 3 with the exception that transcutaneous electrical nerve stimulation (TENS) was added. Thirty (30) and 300 Hz stimulation was used to test the impact on proprioceptive position sense ability. In this experiment the adducted arm posture was used and only the downward direction was tested. In previous studies of 3d proprioception it has been shown that downward movements did not achieve high levels of sensitivity until 4cm given an adducted arm posture (Joshua Klein et al., 2018). Down was chosen as it would give ample opportunity for enhancement to be shown at shorter distances from the reference location. Thus, this direction gave us the most opportunity to see improvements at multiple displacement distances.

Stimulation Parameters

The DS8R produced by Digitimer Ltd (Hertfordshire, UK) was used for these experiments and is approved for human research. For all stimulation experiments the parameters were as follows: 3ma amplitude, 350us pulse duration, biphasic ratio of 100%, and interpulse interval of 350us. These settings were the highest settings that consistently preserved participant comfort throughout the entire experiment with each electrode configuration. The DS8R is triggered by the rising edge of a 5v square wave so an external function generator was used to set the frequency of stimulations. For these experiments a frequency of 30hz or 300hz were used. The D188 remote electrode selector, also produced by Digitimer, was used to select which electrode pair would receive the DS8R's stimulation.

Software

The programs controlling the experiment communicated with an Arduino Nano (Arduino Board Nano, 2017) via serial connection which would select the appropriate electrode and trigger the function generator to start or stop stimulation from the DS8R to the chosen electrode pair at the appropriate time.

This experiment used the same software and hardware setup from prior experiments with the addition of the stimulation. The same shared memory component was used to communicate to a new subsystem that would communicate with and control the stimulation output. This shared memory was then used to send information about the trial that was starting, causing randomization of the stimulation location and allowing for that communication to be sent back to the main program to be recorded. The trial information was used by the stimulation controller to ensure that the trials were balanced, i.e. generating the same number of trials of 'same' and 'different' for each of the 3 stimulation configurations. A serial command transmitted from the main program to the Arduino Nano, running custom software, was used to produce a 5v trigger on the wire connected to the function generator. This signal would cause the function generator to produce a square wave at a specified frequency that would in turn trigger the DS8R to produce the stimulation output. At the same time the serial command from the main program also indicated which electrode pair should be selected. The Arduino set one of the controlling input lines to the D188 high (i.e. to 5v) which would select the specific channel that needed to be stimulated. These determinations by the stimulation control program were then relayed back to the main control program so that it could be written to the output file for later analysis. A diagram of this design and communication channels can be seen in Figure 10.

Electrode Placement

All stimulation was provided via two round 1.25" self-adhesive electrodes ("Axelgaard PALS Electrodes," 2018). Three electrode configurations were examined and a diagram of approximate electrode placements can be seen in Figure 15. Stimulation of the shoulder was done with the electrodes placed approximately 2-3 inches apart along and approximately 1 inch above the scapular spine. This placement was meant to avoid as many cranial nerves as possible while still providing an electro-tactile sensation the participant during stimulation. Two electrodes were also placed approximately 2-3 inches apart on the back of the neck near C2/C3 of the cervical spine meant to stimulate vagal nerve projections that enervate the back of the neck. Forehead stimulation was provided by placing one electrode near the right mastoid process and one on the right forehead above the eyebrow and lateral to the eye (close to the right temple). Typically, this last electrode was adjusted on a subject by subject basis to maximize comfort. These locations were chosen for their proximity to ophthalmic branch of the trigeminal nerve (forehead), vagus nerve as it leaves the jugular foramen (neck), and possibly the accessory nerve but was originally meant to be used as a sham stimulation location (shoulder). Stimulation of forehead and neck locations has shown to be effective in eliciting cortical responses (Tyler et al., 2015). Although not many studies have examined these exact placements and stimulation parameters the theoretical outcomes of this type of stimulation warrant investigation.

When participants arrived for the experiment they would complete their informed consent form and review the task before electrodes would be attached. These would then be tested for comfort starting with a single stimulation pulse then followed by a short (.25-.5 second) higher frequency pulse using either the 30hz or 300hz frequency depending on the group to which the subject which group the subject. Finally, a ~3.5-4 second duration stimulation was given to ensure that the stimulation didn't become uncomfortable because a full trial 3.75s in duration. If at any point during the setup (single pulse, short burst, or full trial length stimulation) the participant reported any sharp pains or discomfort then the electrode placement would be slightly adjusted, and the procedure restarted with single stimulations. Only one participant was unable to complete the experiment due to not being able to find a comfortable location for the electrodes. Once electrode placement was finalized athletic tape was used to secure the electrodes in place on the neck, forehead, and behind the ear. Typically, the electrodes placed on the shoulder were held on by the participant's shirt or the shoulder straps of the chair. Electrodes were periodically checked throughout the experiment to ensure they were holding in place well and were re-taped if needed.

Statistical Analyses

All statistical analyses were conducted in SPSS 25. D' was calculated using the same procedure described in Chapters 2 and 3 (Joshua Klein et al., 2018). Bias (c) was also calculated as described in Chapter 2. Differences in d' as a function of displacement distance was assessed using a three-factor mixed analysis of variance (ANOVA; within subjects factor: distance (1, 2, 3, and 4 cm) and stimulation location (forehead, neck, shoulder); between subjects factor: stimulation frequency (30hz and 300hz). Significant interactions were further analyzed using Tukey's post hoc tests.

Bias was analyzed similarly using a three-factor mixed analysis of variance (ANOVA; subjects factor: distance (1, 2, 3, and 4 cm) and stimulation location (forehead, neck, shoulder); between subjects factor: stimulation frequency (30hz and 300hz)]. Significant interactions were further analyzed using Tukey's post hoc tests.

Results

As expected, proprioceptive sensitivity increased monotonically with distance from the reference location. Figure 16 shows the mean sensitivities for all the stimulation locations (forehead, neck, and shoulder) as well as the stimulation frequencies (30hz and 300hz). A multi-factor ANOVA on distance, stimulation location, and stimulation frequency showed no main effects of stimulation location or stimulation frequency (Figure 16). However, we observed a distance main effect [$F(3, 102)=132.65$, $p<.001$], as was expected. We also found a distance by stimulation frequency interaction [$F(3, 102)=4.38$, $p<.01$]. After collapsing data across the stimulation location variables because of no significant effect's comparisons between 2cm and 3cm distances were made. At the 3 cm distance, performance was significantly higher for 300hz stimulated participants compared to participants receiving 30hz stimulation (see Figure 17); significant with Bonferroni correction (t(29)=3.01. p<.01) while 2cm showed no significant differences.

Figure 18 shows the bias changes as a factor of distance from reference location with all stimulation configurations and frequencies. This shows a peak of bias, c, at 2cm for all data points which then decreases monotonically to the 4cm distance. Bias was analyzed with a multi-factor ANOVA on distance, stimulation location, and stimulation frequency similar to sensitivity. This analysis showed no main effect of stimulation location or stimulation frequency at 30hz and 300hz. There was a main effect of distance [F(3,114)=19.19, p<.001] showing a difference in bias as the distance from the test position increased. Bias did increase from 1-2cm but then decreased monotonically beyond 2cm.

Although direct, statistical comparisons are problematic when comparing this data set to the non-stimulation experiments (Exp. 1, Chapter 3), it should be noted that sensitivity during 300 Hz stimulation appeared qualitatively similar to sensitivity observed in Experiment 1 (Figure 19). Given lower sensitivity for 30hz stimulation at some distances the 30hz stimulation may have had a deleterious effect on proprioceptive sensitivity within this task.

Discussion

Several previous studies have used some form of exogenous stimulation to modulate cognitive function or perception. This study has demonstrated an effective modulation of proprioceptive sensitivity for movements down from a reference location. This direction of movement gave multiple distances at which improvement could be observed because of previously shown poor sensitivity (Joshua Klein et al., 2018). The stimulation location showed no statistical effect on the sensitives of participants while there was significant interaction between the distance from the reference location and the stimulation frequencies used. Furthermore, analysis at individual distances showed a significant difference at 3cm between the 30hz and 300hz stimulation after eliminating stimulation location as a factor. This clearly shows some modulation of proprioceptive sensitivity. Bias was affected by the distance from the reference location but no effect of the stimulation frequency or the stimulation location was shown. Bias is unaffected by the stimulation but is influenced by the distance from the reference location. This is expected because the information available to the participants at each distance changes allowing them to make more decisions based on detectible differences and less on bias. These findings suggest that arm proprioceptive sensitivity can be modulated through the application of TENS targeting cranial nerves.

Electrical stimulation of the nervous system has a long history and is well-known to alter the activation and functioning of cortical and spinal circuits. For example., Transcranial direct current stimulation (TDCS) has recently been used to enhance performance on many cognitive tasks (V. P. Clark et al., 2012; Coffman et al., 2014; Pisoni et al., 2018). Transcutaneous electrical nerve stimulation (TENS), which has typically been used to modulate pain or elicit muscle contraction has more recently been shown to be effective in altering firing patterns of superficially accessible somatic nerves and enhancing sensorimotor functions such as proprioception (Chang et al., 2013; Jung et al., 2017; Junhyuck et al., 2014; Shirazi et al., 2014; Tyson et al., 2013). TENS has more recently been used to investigate cortical modulation and has been effective at eliciting cortical circuit activation (Hulsey et al., 2017; Tyler et al., 2015). With the connection from cranial nerves to the ARAS, long-lasting changes in proprioceptive function, relative to somatic stimulation, may be possible with this technique that could aid in task learning as well as rehabilitation.

The trigeminal nerve as well as the vagus nerve connect with the locus ceruleus (LC), a component of the ARAS, which releases noradrenaline to many portions of the cortex via a wide array of synapses. This ARAS activation can lead to general enhancement of cognition and learning as shown through pharmaceutical studies (Sara, 2009). Anything that can cause a modulation of these brain structures could theoretically have the same or similar effects, including pharmaceuticals. However, increasing activation of these systems with pharmaceuticals can also alter functioning of brain areas other than those that are the targets of modulation, due to the systemic means of delivery for those agents. Cranial nerve stimulation may be able to more directly alter functioning of these areas, enabling similar enhancement effects without the systemic side-effects.

Stimulation parameters

Of the few studies using TENS on cranial nerves, such as the trigeminal (TNS) or vagus nerve (VNS), some have shown behavioral changes to stress responses although functional enhancements for an active, functional, task were not reported (Tyler et al., 2015). As discussed in Chapter 1 many different methods exist for using TENS and most of these have focused on disruption of activity related to disease states. Currently, TENS is approved for use peripherally to help reduce muscle pain and devices for these treatments can be bought off the shelf at many stores. How TENS was used previously was shown to be very effective at disrupting the peripheral pain signals however, the use of TENS on superficial cranial nerves is a somewhat new use of the technology and there are few publications focused on using it for enhancement as attempted in this study. Very recently it has been shown that VNS paired with tactile training helped to improve lost touch sensation in post-stroke patient (Kilgard et al., 2018).

There is very little consensus on what parameters may produce desired effects and that feature space would likely be more limited than stimulation to create a disruptive effect. This study tested the effects of stimulation frequency while all other parameters (current, pulse length, biphasic pulse gap, and aspect ratio) were held constant in order to view the influence of only a differing rate of stimulation on proprioception. Implanted vagal stimulation devices have been approved by the FDA to use frequencies between 20 and 30hz for clinical use (Groves & Brown, 2005). While the implanted nerve cuffs and TENS are quite different stimulation at this frequency could have promise because of it's previously shown clinical effects. Other work has shown that higher frequency stimulation can have significant impacts on cortical processing, most profoundly the sympathetic nervous system (Tyler et al., 2015). A 300hz stimulation along with the 30hz stimulation was used while holding other parameters the same, importantly amplitude, to maintain comfort for participants during the experiment. Three milliamps of current produced by the DS8R was near the comfort threshold for nearly all participants with proper electrode placement. Only one participant did not complete the study because of aversion to the stimulation during the setup and initial testing of the stimulation.

Stimulation Locations

Electrode placement were chosen to target the trigeminal nerves on the forehead and cranial nerves on back of the neck. Stimulation provided to the shoulder was meant to be a sham location that would not activate cranial nerves however the shoulder stimulation showed no significant difference to the other locations. The specific location of stimulation did not show any significant differences in proprioceptive sensitivity or bias. This may have been caused by the stimulation reaching targets that were unaccounted for that were as stimulation on the neck will also stimulate other spinal nerves and possibly the accessory nerve. Stimulation on the forehead traveled from the forehead to near the mastoid process which includes other cranial nerves (notably the facial nerve and the vagus nerve). This type of spread is common among stimulation paradigms as the current can easily spread through soft tissue (Miranda et al., 2006; Underwood, 2016).

Many the nerves that were targeted, notably the trigeminal and vagal nerve project to the LC that controls noradrenergic release and contributes to the ARAS activity that leads to widespread arousal changes and more cortical activity. Prior work has shown the effectiveness of modulating stress response correlated to activation in these structures with vagal nerve stimulation (Tyler et al., 2015) and more recent work has shown that the LC activity can be driven by vagal stimulation (Hulsey et al., 2017).

Limitations

This study was limited in its ability to directly compare the data collected with stimulation to a sham location or data from non-stimulated participants however data from a previous study collected in the same way can provide information to inform future studies. While no statistically analysis was done a visual comparison of the data from the non-stimulated paradigm and the data produced when 300hz and 30hz stimulation was applied (Figure 18). Non-stimulation data presented was first presented in (Joshua Klein et al., 2018).

The testing of different stimulation parameters is a current limitation of our understanding of the effects this type of stimulation will cause at a functional level. There is activation of the ARAS in some way but the specific effects of the stimulation is still being explored.

Future Directions

Providing a control in TENS studies can be difficult because the stimulation can be felt and changes to parameters can be readily felt by participants. Simply reducing the amplitude of stimulation to a very low level may not be enough to completely blind the participants to the expected outcomes because it still provides different levels of sensation. A non-stimulated paradigm may be better suited for these types of studies as a between group comparison. This would blind participants to the stimulation, or lack thereof, they were receiving because they don't have a reference for the sensations produced by stimulation. Future work could be done to produce a quality sham or non-stimulated group as a comparison to any stimulation parameters.

Although some work has been done to quantify the effects of TENS when applied to cranial nerves there is still a lack of understanding of what stimulation parameters will be effective in eliciting modulation. With nerve cuffs it is much more well understood what fibers are being activated by different amplitude and frequency stimulations (Groves & Brown, 2005). This same type of understanding will be invaluable to future studies attempting to find parameters of stimulation to produce specific, desirable effects and can only be done with many more studies to map the feature space of TENS. As of now the specific effects of altering any single stimulation parameter is unknown but developing an understanding of those effects would allow stimulation to provide a new pathway for psychiatric treatments while possibly avoiding unwanted side effects. Previous research has shown the effectiveness of modulating the activity of the ARAS and TENS provides an avenue to explore the possibility of doing just that without drugs.

Stimulation was shown to cause a modulation in proprioceptive sensitivity through an interaction between distance and frequency. Specifically, at the 3cm mark there was a significant difference in sensitivity. The bias was unaltered by stimulation frequency but was influenced by the distance from the reference location. The effect of stimulation shows promising results in being able to modulate the activity of cortical structures to alter sensitivity of sensory systems. With more work optimal parameters could be uncovered which could result desired (positive) changes in sensitivity. This alteration could be done to enhance recovery of function after injury, or even athletic performance.

CHAPTER 5 DISCUSSION

Studies conducted in 2d have shown that arm proprioception is both location and direction dependent. The experiments discussed in Chapter 2 and Chapter 3 further expand upon the current understanding of proprioception by characterizing this sense in a 3d workspace. A 7-DoF robotic arm was used to control the position, movement, and configuration of each participant's arm to characterize differences in sensitivity and bias. Movements in the 2d plane (leftward/rightward, forward/backward) were examined in order to validate the task used here against those described in previous literature. In addition, upward and downward movements were also examined as they had not previously been characterized. Previous 2d experiments had constrained arm movement to the horizontal plane and had demonstrated specific dependencies as described above, but the generality of these findings could not be assessed due to the use of a single posture (Dukelow et al., 2010; Simo et al., 2014; Wilson et al., 2010). As a result, in the studies described here, sensitivity and bias were also tested with an adducted and abducted arm posture, the latter simulating conditions in previous 2d experiments. Differences in sensitivity were found between movement direction and arm posture that were consistent with previous 2d studies that used an abducted posture (Wilson et al., 2010). Experiments with an adducted posture showed differences in sensitivity that had not previously been explored in a passive task. Overall, arm proprioceptive sensitivity was shown to be both anisotropic and configuration-dependent in 3d space.

Stimulation using electricity has long been known to cause modulation of nerve and cortical activation and has been used in a wide range of applications. The tools available for assessment and modulation of nervous system activity have become more refined as technology advances. More recently, transcranial direct current stimulation (TDCS) has become a popular tool for modulating some cortical circuits and providing beneficial effects for conditions such as multiple sclerosis (MS), Parkinson's disease (PD), and schizophrenia (Benninger et al., 2010; Boggio et al., 2006; Brunelin et al., 2012; Cuypers et al., 2013; Ferrucci et al., 2014; Fregni, Boggio, et al., 2006; Göder et al., 2013; Mori et al., 2013; Smith et al., 2015; Vercammen et al., 2011). TDCS has also been shown to be able to cause enhancement of some cognitive tasks although the precise method of action is unknown (V. P. Clark et al., 2012; Coffman et al., 2014; Pisoni et al., 2018). Although TENS has historically been used to modulate pain and to elicit muscle contractions (i.e. Functional Electrical Stimulation (FES)), it has also recently been used for sensorimotor enhancement by applying it to peripheral nerves responsible for sensory information transmission and has been shown effective in enhancing posture, balance, and proprioception (Chang et al., 2013; Jung et al., 2017; Junhyuck et al., 2014; Shirazi et al., 2014; Tyson et al., 2013). Although TDCS and TENS deliver electricity to the nervous system differently, i.e. as continuous direct current or as pulsed, alternating current, both can alter functioning of the nervous system. A simulation study as well as a study on mice has also shown that little of the current from TDCS may actually be making it through the skull thus it has been suggested that this stimulation could be activating superficially available nerves such as the trigeminal or vagus nerve (Miranda et al., 2006; Vöröslakos et al., 2018). TENS as used in this study was used to target these cranial nerves. These nerves make connections to the ascending reticular activating system (ARAS) and based on pharmaceutical studies (Sara, 2009), endogenous activation of these nerves could in principle modulate cortical activity to cause enhancement of cognitive functions. The modulation of the ARAS via cranial nerve activation the focus of many current neuromodulation techniques and could be a powerful tool for clinical treatments, cognitive, and sensorimotor enhancement (Groves & Brown, 2005; Hulsey et al., 2017; Kilgard et al., 2018; Steenbergen et al., 2015; Yakunina, Kim, & Nam, 2017).

The studies presented here clearly show an effect of direction of movement and arm posture on proprioceptive sensitivity as well as an effect of TENS on sensitivity. A more complete understanding of proprioceptive differences could help to better quantify deficits in clinical populations as well as provide a baseline from which to measure proprioceptive enhancement. TENS modulation of proprioceptive sensitivity may be an effect of ARAS activation via stimulation of cranial nerves and provides a foundation for future studies into enhancement of sensorimotor activities.

Sensitivity anisotropies

Using the 3d paradigm for proprioceptive assessment movements left and right from the starting location were the most sensitive approaching maximal sensitivity at 2cm, forward and upward were the next most sensitive approaching maximal sensitivity at 3cm, and downward and backward were the least sensitive requiring position change of 4cm to reach similar sensitivity. These anisotropies did not match previous literature which had shown forward and backward being more sensitive than left and right movements (Wilson et al., 2010). Also surprising was the sensitivity differences between upward and downward directions of movement with only downward movements showing significant reduction in sensitivity. Previous studies have shown less representation of those directions in the cortex of non-human primates (Tillery et al., 1996). The low sensitivity seen for downward motion is expected given the previous studies, but upward sensitivities did not follow the same pattern of decreased sensitivity. In comparison to previous proprioceptive sensitivity studies one large difference between our methods was the posture of the arm during the testing, indicating further experiments using a more similar posture are needed to compare with previous test procedures.

Posture dependence

Arm configuration has been shown to be important for reaching tasks and in simulations of proprioceptive contributions to reaching (G. A. Apker et al., 2011; Gregory A Apker & Buneo, 2012; Gregory A Apker et al., 2010; Dukelow et al., 2010; Ghez et al., 1995; Gordon et al., 1995; Sainburg et al., 1995; Shi & Buneo, 2012; Wilson et al., 2010). Within the 3d proprioception task, the anisotropies did not match with expected values based on previous literature which led us to question the effect of arm posture on these sensitivities. By creating a sling to support the arm of the participant during our task we could still measure passive proprioception while more closely matching previous testing conditions from prior studies. The resulting sensitivities were much more closely aligned to previous findings. Differences between the results showed that posture has a significant effect on the sensitivities of position sense. This had previously been hypothesized based on simulation and reaching experiments but had never been directly tested.

The ability to change arm configuration during testing without altering the location of the workspace is also possible with this task. With 2d assessments the placement in the workspace is naturally confounded with the posture of the arm because of the constraint that the arm must be held horizontally. By extending testing into 3d space with extra degrees of freedom the posture can be tested within the same locations in the workspace while altering the geometry of the arm during those movements. Evidence from this study suggests that sensitivity is related to the geometry of the arm and muscle spindle afferent differential activation within those different postures.

Stimulation

Stimulation frequency did affect sensitivity at 3cm however this appears to be caused by a decrease in sensitivity with the 30hz stimulation. This effect may have been caused by modulation of RAS via activation of cranial nerves, however, the stimulation was also suprathreshold and the participants were very able to feel the stimulation as it was occurring. This stimulation, as well as stimulation at 300hz, may have been providing another sensory signal to attend to that may have detracted from performance in the proprioceptive task. The parameter space for TENS is large and not well characterized, especially in the context of cognitive enhancement. Stimulation parameters that are sub-threshold for sensation may be able to cause similar modulatory effects which would reduce distraction as a possible confounding effect of the stimulation used in these experiments.

Bias did not show any changes between the stimulation frequencies or locations. Interestingly, the pattern of bias across distances for the down direction was similar in experiments with and without stimulation. However, in experiments without stimulation, bias did appear to vary across directions, implying that subjects used different strategies for different directions in this task. When all directions and distances were considered there was a moderate negative correlation between sensitivity and bias (~ -0.5) meaning that as information about the position of their hand increased (as implied by greater sensitivity) their strategy changed from being slightly conservative (i.e. tending to respond ‘different’) to being relatively unbiased or slightly liberal.

No effect was shown between the different stimulation locations tested (forehead, neck, and shoulder). Based on the locations of the stimulation we were using activation may have had many common targets. There are afferents of the vagus nerve in the ear lobe that could have been easily stimulated by the forehead stimulation. Stimulation on the neck could have activated spinal nerves which innervate some of the same brainstem targets as the vagus and trigeminal nerves including the trigeminocervical complex (Akerman, Holland, & Goadsby, 2011). Shoulder stimulation as initially expected to act as a sham stimulation site however there is evidence that the accessory nerve also has sensory components that may have been activated by the stimulation and project to similar structures as the vagus nerve (Bremner-Smith, Unwin, & Williams, 1999).

Clinical Relevance

3d proprioception

Despite its importance in normal sensorimotor functioning, proprioception is often only assessed in a very coarse manner in clinical settings, typically assigning patients into categories of ‘intact’, ‘impaired’, or ‘absent’ (Simo et al., 2014). These types of assessments are done to quickly and broadly identify the deficits of a patient and doesn’t quantify the deficit very precisely. Typically, the assessment is either a single joint, commonly a toe, being moved and having the patient determine the direction of movement or a position matching task where they are asked to match the position of their opposite arm that has been passively moved. This type of testing has been shown to have questionable inter and intra-rater reliability (Carey, 1995; Dukelow et al., 2010; Lincoln et al., 1991; Simo et al., 2014). Robotic assessment provides a more detailed view of proprioception allowing for quantification of deficits, or normal function, that can observe smaller changes in sensitivity, be more repeatable, and more reliable than traditional clinical assessment. Robotic assessments such as these can then be used to observe differences in experimental conditions for rehabilitation paradigms to determine recovery on a finer scale than typical, non-instrumented, assessments. Although these methods for assessing proprioception are more precise than some clinical assessments their usefulness in the clinic could be limited due to the somewhat longer period of time required for such assessments.

Stimulation

The trigeminal and vagus nerves have been shown to have modulatory effects on the LC and the noradrenergic pathways (Hulsey et al., 2017). This shows that hypothetically that exogenous stimulation of trigeminal and vagus nerves could have modulatory effects on ARAS and could be used as a treatment for some neurological disorders. Cervical spinal nerves have also been shown to have connections to the trigeminocervical complex that contains secondary connections to the LC and RAS system (Akerman et al., 2011). These pathways of activation could also be responsible for cognitive enhancement through modulation of the trigeminal, vagus, and cervical nerves

(Sara, 2009). Many studies have shown benefits of this type of stimulation on neurological symptoms although a direct link between the two is still untested (Benninger et al., 2010; Boggio et al., 2006; Cook et al., 2013; Cuypers et al., 2013; C. M. DeGiorgio et al., 2009; Christopher M DeGiorgio et al., 2013; Fan et al., 2018; Ferrucci et al., 2014; Fregni, Boggio, et al., 2006; Groves & Brown, 2005; Kulju et al., 2018; Mori et al., 2013; Nemeroff et al., 2006; Michael A Nitsche & Paulus, 2009; Paulino Trevizol et al., 2015; Sackeim et al., 2001; Sadler et al., 2002; Schrader et al., 2011; Soss et al., 2015). Non-invasive stimulation of these cranial nerves may provide an excellent clinical target for modulation of cortical circuits central to these debilitating diseases.

Regarding enhancement of proprioception specifically, TENS has been used in the periphery to enhance proprioception but the stimulation was used on peripheral nerves or using a sock with embedded electrodes and wasn't targeting cortical structures but instead the sensory signals being sent via those peripheral nerves (Chang et al., 2013; Jung et al., 2017; Junhyuck et al., 2014; Shirazi et al., 2014; Tyson et al., 2013). The stimulation used in the present experiments wasn't targeting the nerves of the upper limb to alter the signals from the proprioceptive receptors but instead was stimulating cranial nerves to modulate central nervous system activity. In this way, the stimulation is believed to be affecting the manner in which the cognitive system interprets incoming sensory signals. This change in targets away from peripheral nerves could be another channel that clinicians could use to ameliorate proprioceptive deficits.

One large reason that TENS is an attractive target for clinical applications is that electrical devices like the ones discussed in this dissertation are very easy to use and test for effectiveness on individuals as well as being much cheaper to develop. Often people seeking help for psychiatric disorders will need to try several different drugs and/or dosages before finding something effective. A small number of cases are even resistant to any type of drug treatment. Psychiatric drugs also tend to take time to reach an effective concentration and have a lot of negative side effects during that time. Many drugs commonly used for depression can cause or increase depressive symptoms or treat different subcomponents of the disorder at different rates leading to many negative consequences. It's not clear that even if these devices prove their effectiveness for psychiatric disorders that their effects will be instantaneous, but they do avoid off-target effects of many of the commonly used medications today. A main target for the treatment of depression is serotonin using selective serotonin reuptake inhibitors (SSRIs) but it can also cause side effects because of serotonin receptors' presence in the digestive tract. Oral medications will have a systemic effect that can cause these off-target consequences. Electrical devices to stimulate peripheral nerves are already available in many stores for the treatment of muscle pain. The cost to develop the same technology with different stimulation parameters will take time and money, but nothing compared to the time and money required to develop and test a new psychiatric medication. TENS usage could be another way of altering function if medications are ineffective for an individual or used in conjunction with medication to achieve more robust effects.

Limitations

The three-dimensional paradigm that was developed for these experiments to expand proprioceptive assessment does allow for arbitrary angles and postures of the arm to be tested. In these experiments it was testing only four different distances (1-4 cm from the reference location). The experiment could be expanded to test positions between those distances, but the paradigm can only test at discrete distances rather than continuous results that can be gathered from arm matching or other tasks that allow participants to respond, or move, to any position within the workspace. Results from this discrete paradigm did align within expectations from previous literature that used a more continuous paradigm (R. J. van Beers et al., 1998), suggesting that the results may carry some validity and the paradigm has utility in certain contexts.

This task also contains a memory component between the endpoint of the arm being at the reference position before moving to a distractor position and then back to the judgement position. Other studies have been conducted with similar memory components and shown that performance is similar between non-memory and memory required tasks (Wilson et al., 2010). If this test was conducted with stroke survivors, then it would be important to ensure that memory deficits were not a factor in performance for this assessment.

The stimulation provided for the last experiment was limited in the range of parameters that were tested. There is some evidence for TNS being effective at producing modulatory effects on the noradrenergic system with a 7-11khz frequency and stimulation of 100 or 120hz has been effective in drug-resistant epileptic patients (Christopher M DeGiorgio et al., 2013; Tyler et al., 2015). Only using 30hz and 300hz stimulation does provide some information but other frequencies or parameter sets may have different effects and may provide significantly different results even with minor changes to stimulation parameters.

We theorized that modulation of cranial nerve activation would cause a modulation of the RAS. This may still be the case, but it seems that the locations we were stimulating may have all been having some impact on the RAS which may have led to the same effects on proprioceptive sensitivity regardless of the stimulation location. Trigeminal and vagus nerves have been shown to have connections to RAS and can cause modulatory effects (Tyler et al., 2015). Stimulation provided on the shoulder, while originally chosen to avoid sensory afferents, may have activated afferents of the accessory nerve which has some connections in common with the vagus nerve and could possibly cause modulation of cortical circuits via similar sensory pathways (Bremner-Smith et al., 1999). Overall the stimulation location as was used in these studies may have been activating overlapping systems that all had some influence over RAS activity leading to similar results across all locations. The specific pathway of modulation may be unimportant as activation of the RAS through any pathway may have indistinguishable but still beneficial effects.

Future studies

Using a discrete 2AFC task does provide quality information while eliminating many of the confounding aspects of other studies however other paradigms do allow for more robust data to be collected. Using a similar equipment set up it would be possible to alter some parameters and collect other data that may allow for more flexibility in response from the users. One such way to adapt the task would be with a passive task where the arm could be driven out to a passive position, brought back to the starting location, and then slowly moved on a path through the target location. Participants could be asked to stop the robot at any point along the path when they felt like they had reached the target location. This would maintain the passive aspect of the task and provide more continuous results about position sense instead of only testing at discrete, 1-4cm from reference, locations.

This entire task also eliminated any vision of the target throughout the experiment to make sure that position and arm configuration would not be influenced by it. Some technology pieces could be added to allow for a visual reference of the target location without the arm posture or position being directly visible. Using a VR system would allow for manipulation of the virtual environment to measure the effect of different visual components on proprioceptive sensitivity using this task. 2d tasks have used similar VR environments to measure differences before and expanding that into 3d could provide similar additions to our understanding of proprioception as the studies presented in this dissertation.

In the development of this paradigm and deciding to explore 3d space it was necessary to limit the number of directions tested while also collecting data to fit with previous 2d studies. By duplicating 2d results and adding upward and downward motion the 3d aspects of the workspace could be compared to prior work. These cardinal directions are intuitively easy for participants to understand and establish good baseline measurements for future studies. A rotation of those directions could have been done instead, testing 45° oblique angles between the cardinal directions. This would be useful to do in the future as a way to produce a more complete understanding of proprioceptive sensitivity in different directions. Based on previous studies of visual as well as haptic information processing it would be expected that there would be decreased sensitivity in these directions because of the oblique effect (Gentaz, Baud-Bovy, & Luyat, 2008; B. Li, 2003). The oblique effect has been shown as a reduction in sensitivity for visual sensitivity as the movements vary away from cardinal directions. This has been argued to be produced by cortical representations of information that are influenced by using cardinal directions as a type of baseline to compare the oblique directions against (Gentaz et al., 2008). The same type of effects have been seen in haptic experiments however the information provided may be more related to the gravitational vector and torques providing information about the cardinality of those movements (Gentaz et al., 2008). A future experiment exploring the oblique angles could further explore this oblique effect in passive proprioceptive sensitivity to elucidate if the effect is still present in tasks that eliminate active reaching as a component.

The paradigm developed for the experiments presented in this dissertation uses constrained movement to measure proprioceptive sensitivity. Some prior studies do study proprioception of individual joints which is more constrained than the position sense assessment here, but the movement still does eliminate the wrist as a location where movement could occur when using the trough in the experiments. A removal of the constraint on wrist movement may create a more natural motion for proprioception assessment. This would be easily adapted from the current study as all the current procedures could be used with the only change being removal of the trough and a bare handle being installed instead. This manipulation may result in increased sensitivity because of the ability to use more proprioceptive receptors in the assessment of position.

Although the signal produced may be less distinguishable from noise for an individual proprioceptor, they may allow for a more accurate estimate through integration of multiple signals. However, if those signals fall well within the noise limits of the receptors then it may result in a net loss of sensitivity because that noise could become a more dominant factor in position estimates even when accounting for more receptors being available. Determining the role of additional degrees of freedom of movement on proprioceptive sensitivity will be a focus of future investigations.

Currently there are a lack of studies that have explored the full feature space that is possible with TENS of the trigeminal or vagus nerve. Many of the parameters that are starting to be used to modulate activity of sensory or cognitive functions are using parameters of stimulation from prior experiments that were very effective as a disruption of endogenous signals. Using these same types of signals will most likely result in disruption in the same way those studies did. Future studies should attempt to find alternative parameter sets that provide enhancement instead of disruption of performance.

Activation of the ARAS may result in increased generalized arousal that can lead to better cognitive performance (Sara, 2009) and may be helpful in learning new sensorimotor tasks, as has been shown with TDCS and VNS (V. P. Clark et al., 2012; Kilgard et al., 2018). Proprioception may be affected in a similar manner, where sensitivity may be able to be trained more effectively with TENS or some other exogenous stimulation. The current experiments used a task that was performance based and did not assess learning. Performing a similar experiment where individuals practice over the course of several days with stimulation may show effects of stimulation on learning. During learning tasks such as this it is typically accepted to provide feedback on correct or incorrect responses however a measurement of improvement without that feedback may also show learning effects simply because of practice of the paradigm and comfort of the task.

Variability in the amplitudes, frequencies, biphasic ratios, and inter-pulse intervals between studies can all influence outcomes. A dose response curve has not been shown for TENS or TDCS. Some studies showed that different fibers are activated by differing amplitudes and frequencies of stimulation (Groves & Brown, 2005). This may result in a very complicated feature space that isn't necessarily describable with dose response curves. The lack of dose response curves may simply be due to the scarcity of current literature on the subject. Producing knowledge about dose responses may be a difficult task, especially with individual differences in reaction to stimulation (L. M. Li, Uehara, & Hanakawa, 2015). This becomes more difficult because some studies don't report some key components of their stimulation parameters such as pulse duration, pulse phases (mono or biphasic), biphasic ratio, and inter-pulse intervals. Duration and frequency are typically reported, but that can only provide so much information about the specific waveform being used for stimulation.

As enhancement becomes a larger field of study, the necessity to move away from previous parameter sets that were devised to cause disruption in favor of stimulation that has shown promise for enhancement will require a trial and error approach. The reporting of these parameters will be paramount in promoting replicable research and finding parameters that work to provide enhancement in the future.

The two topics explored in this dissertation work to understand the complex feature space that is sensorimotor activity and cortical modulation. The ability to more completely understand, and possibly manipulate, both could facilitate enhancement and recovery of proprioceptive function. The study of proprioception in 3d space is important, despite its challenges, as even marginal increases in rehabilitation success can have profound effects on recovery that may otherwise go unseen with current testing methodologies. Similar advances in the use of stimulation paradigms could also provide benefits to patients, even if only to reduce unintended effects of medications currently in use and provide another means of modulating activity therapeutically.

CHAPTER 6 FIGURES

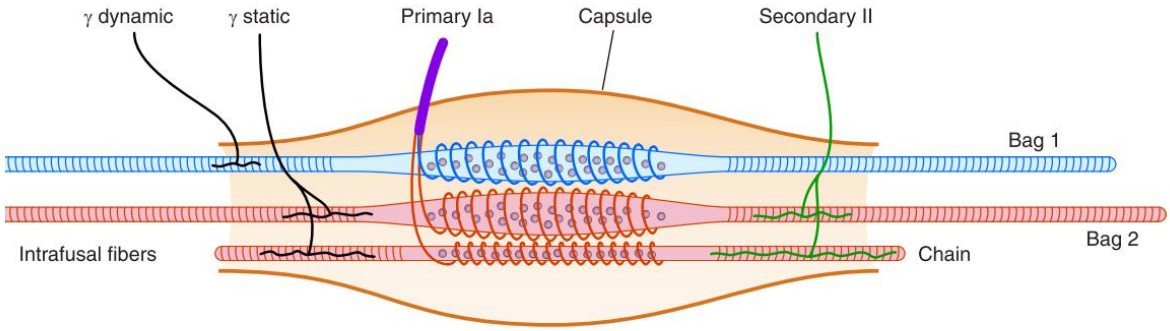

Figure 1 - Diagrammatic representation of mammalian muscle spindle. The intrafusal fibers include the large nuclear bag 1 and bag 2 fibers together with the smaller nuclear chain fibers. Ends of the bag fibers extend beyond the capsule while chain fibers lie within the limits of the capsule. Large, group Ia afferent fibers terminate as primary endings, making spiral terminations around the nucleated portions of all three intrafusal fiber types. Smaller, group II afferent fibers terminate as secondary endings, lying to one side of the primary endings and supplying bag 2 and chain fibers. Gamma dynamic (γ dynamic) fusimotor fibers innervate bag 1 fibers, while gamma static (γ static) fusimotor fibers innervate bag 2 and chain fibers. Figure adopted from (Proske & Gandevia, 2012)

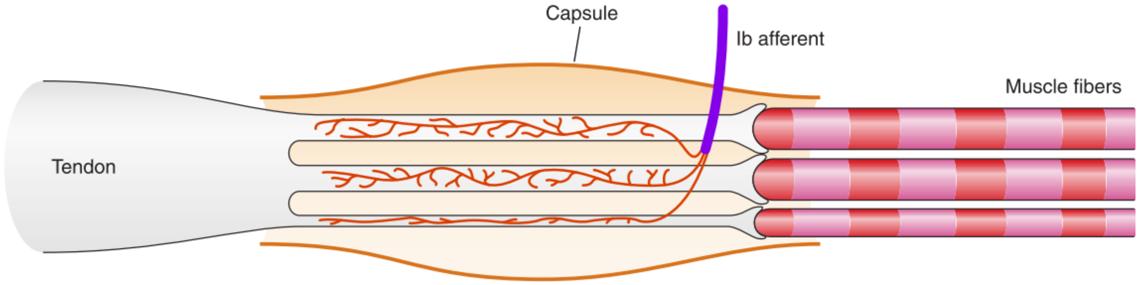

Figure 2 - Diagrammatic representation of mammalian Golgi tendon organ. The Group Ib axon penetrates the receptor capsule and branches, each branch terminating on a tendon strand that is attached to a muscle fiber. A typical tendon organ has 10 or more muscle fibers attached to it, each fiber belonging to a different motor unit. Contraction of a motor unit supplying a tendon organ stretches the tendon strand to which its muscle fiber is attached, generating activity in the Ib axon. Figure adopted from (Proske & Gandevia, 2012).

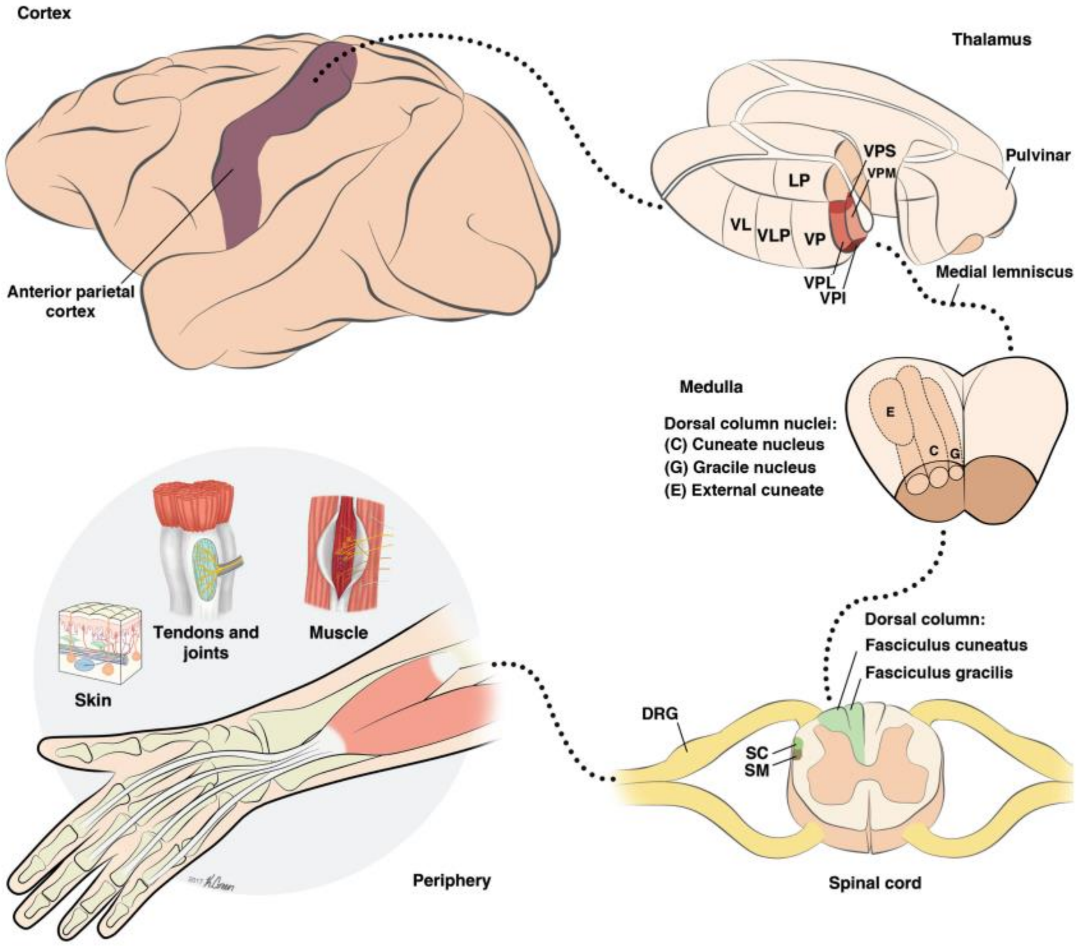

Figure 3 - Pathways from somatosensory periphery to cortex. Afferent fibers at the periphery bundle in fascicles that join to form the nerves. Afferent cell bodies are gathered in the dorsal root ganglia (DRG). When entering the spinal cord through the dorsal root, afferent axons branch, sending one projection to the dorsal horn and one projection to the dorsal column nuclei (DCN) through the dorsal column. The DCN projects contralaterally through the medial lemniscus to the ventroposterior complex of the thalamus, which in turns relays the information to cortex. Abbreviations: Dorsal root ganglion (DRG); spinomedullothalamic (SM), and spinocervicothalamic (SC) tracts. Thalamus: ventral posterior (VP), posterolateral (VPL), posteromedial (VPM), posterior inferior (VPI) and posterior superior (VPS) nuclei, posterior division (VLp) of the ventral lateral nucleus (VL), lateral posterior nucleus (LP).

Adopted from (Delhaye, Long, & Bensmaia, 2018)

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Figure 4 – An example of procedure for the big toe localization test. Patients must determine the direction of movement without the use of vision.

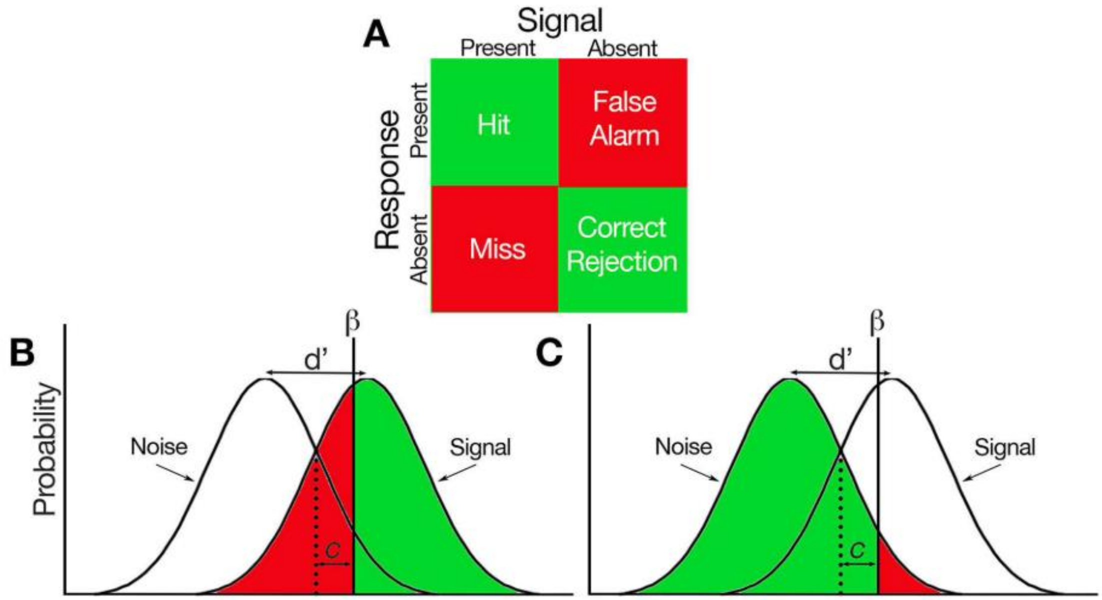

Figure 5 – Signal detection theory measures (A) Response matrix of all signal-response combinations that can be made in a binary decision task. Green indicates correct decision, red indicates incorrect decision. (B) Proportions of hits and misses represented under the signal distribution. β reflects the subject criterion, c reflects bias, and d′ reflects sensitivity which represents the difference in position between the two distributions. (C) Proportions of false alarms and correct rejections represented under the noise distributions. Figure adopted from (N. D. Anderson, 2015).

Figure 6 – Human-robot coupling at the reference position. Photograph used with permission of participant.

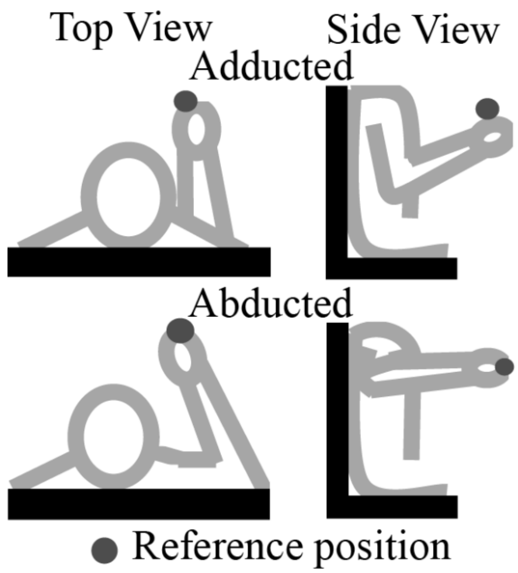

Figure 7 – Arm postures examined in experiments 1 & 2. Adducted was only posture used in experiment 3.

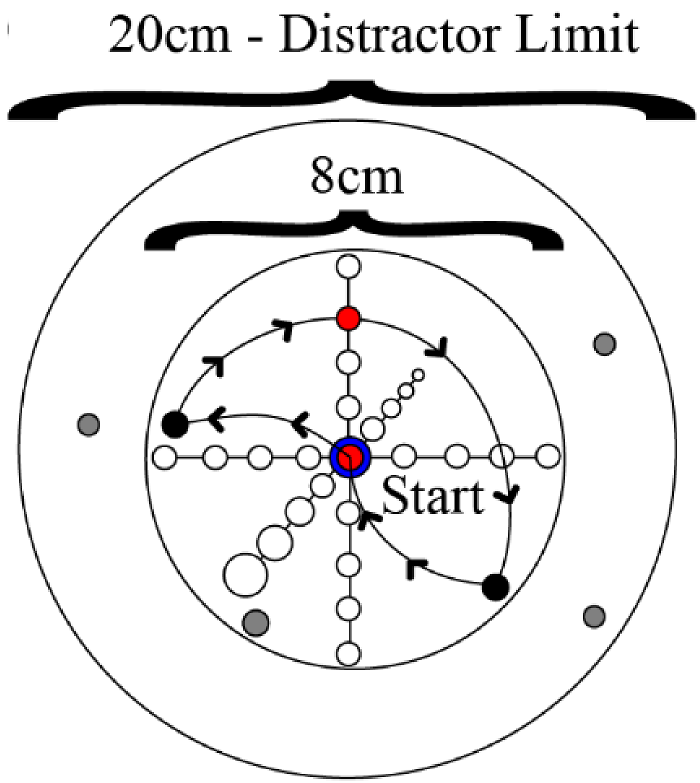

Figure 8 – Location of judgement positions and via points (i.e. distractor positions) with respect to reference position. An example path taken by the robot on a single trial is also shown (arrows). Target positions for all 6 directions tested shown. (hollow circles). Grey filled circles show some distractor positions.

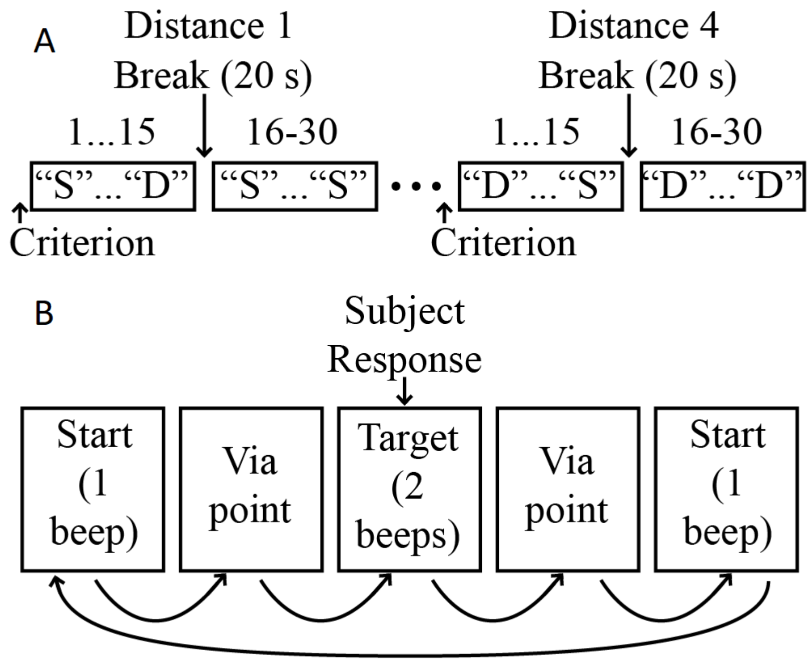

Figure 9 – Experimental protocol. (A) Four distances were evaluated for each direction, with distance order randomized across directions. For simplicity, only two disatnces are shown. "S": same; "D": different. (B) Sequence of events for single trial.

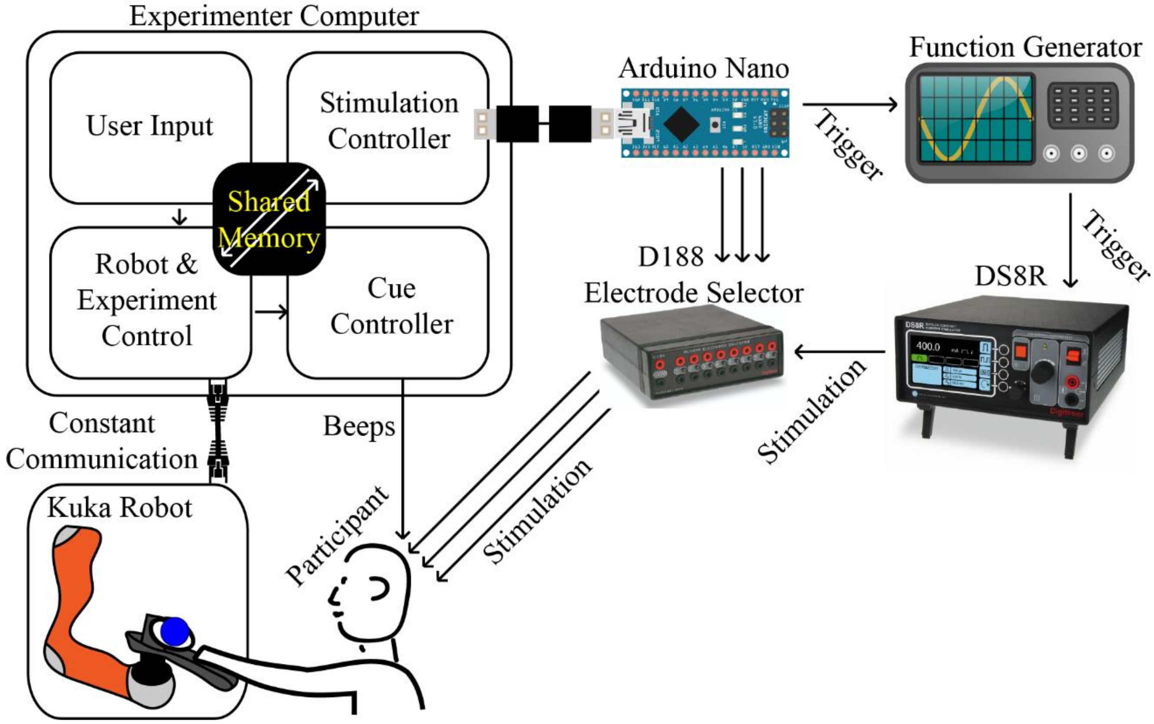

Figure 10 – Block diagram of software and hardware experimental components including TENS stimulation.

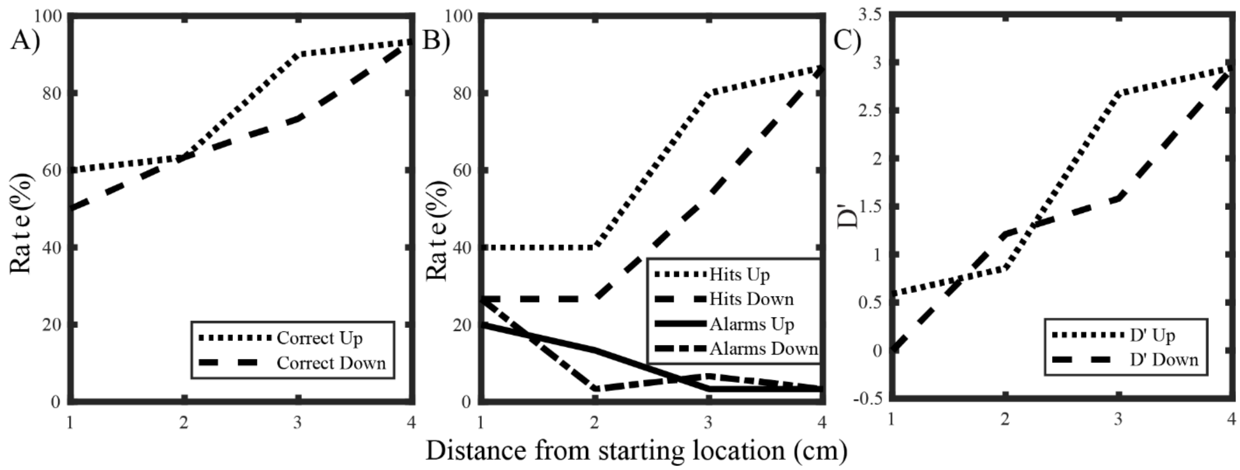

Figure 11 – Single participant example data analysis comparison. Percent correct (A), hit rate and false alarm rate (B) and d' (C) for a single subject. Data for the upward and downward directions are shown.

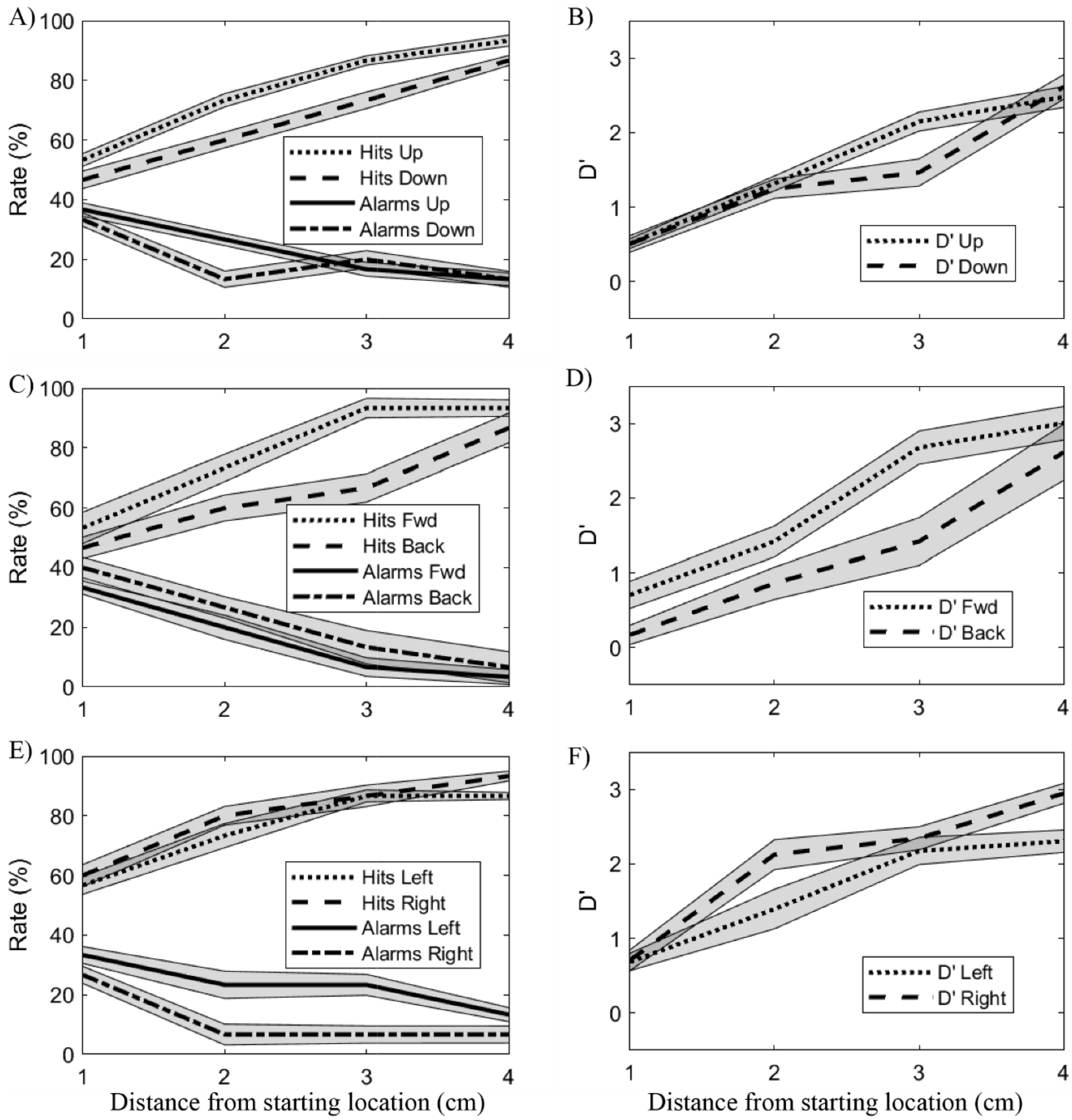

Figure 12 – Percent correct vs sensitivity group means. Mean (±SEM) hit rates, false alarm rates, and d' values for all subjects. (A,B) Upward and downward directions. (C,D) Forward and backward directions. (E,F) Leftward and rightward directions.

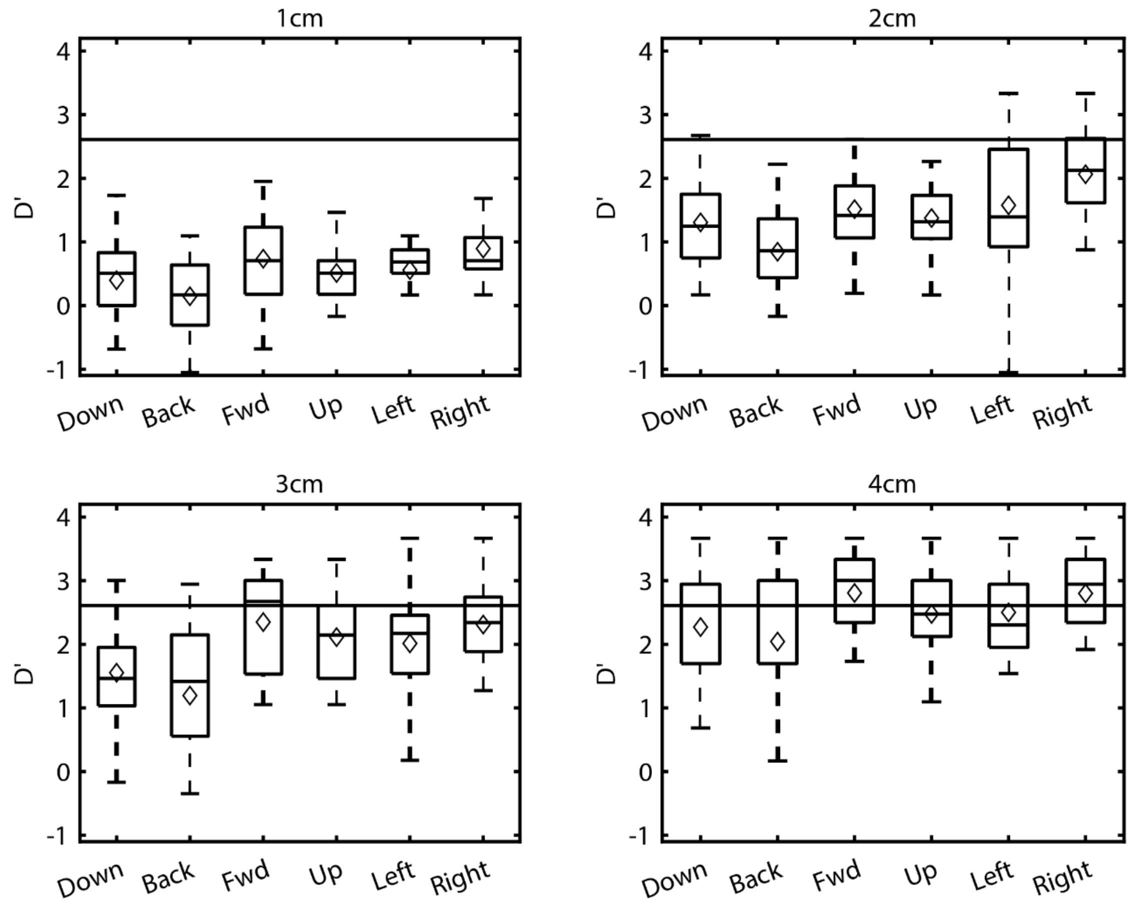

Figure 13 – Boxplots of the sensitivities (d') at each distance and direction for all subjects. Corresponding mean sensitivities (diamonds) are superimposed on each boxplot. Solid line represents grand median of all directions at the 4cm distance.

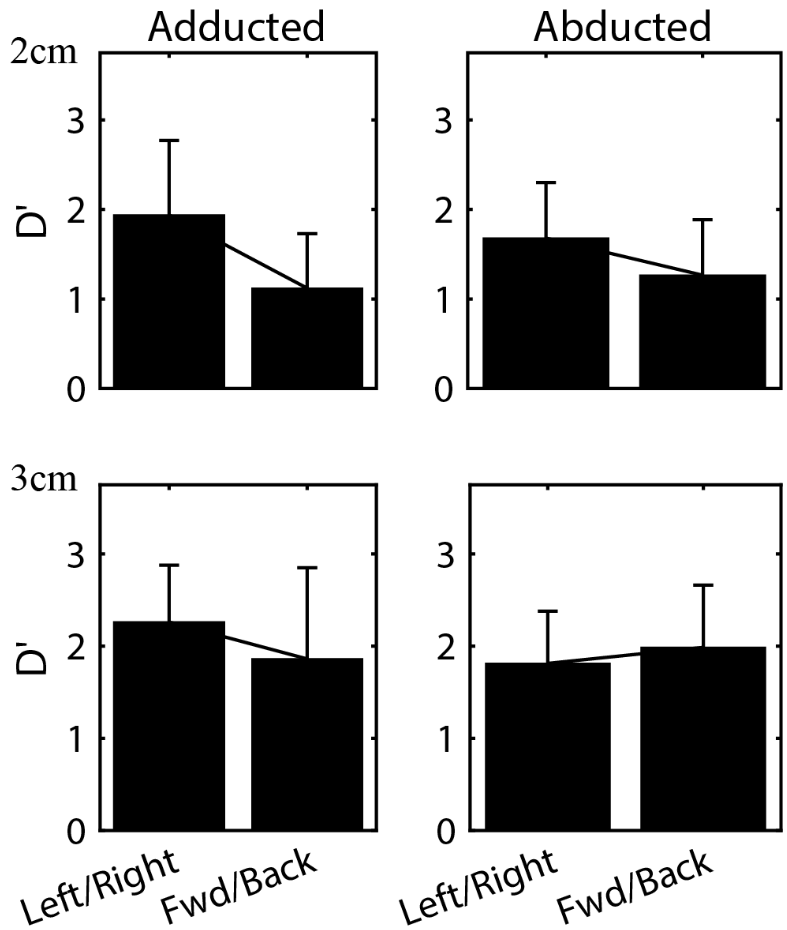

Figure 14 - Mean (±SD) sensitivities for the leftward/rightward and forward/backward axes in both arm postures. Data for all subjects at the 2 and 3 cm distances are shown.

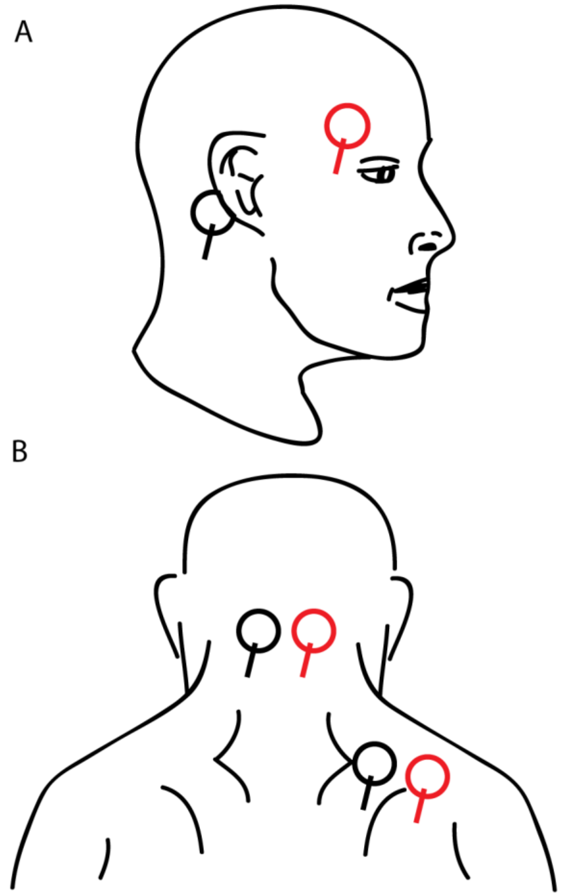

Figure 15 –Approximate electrode placement locations. (A) forehead and behind ear, (B) neck, and shoulder.

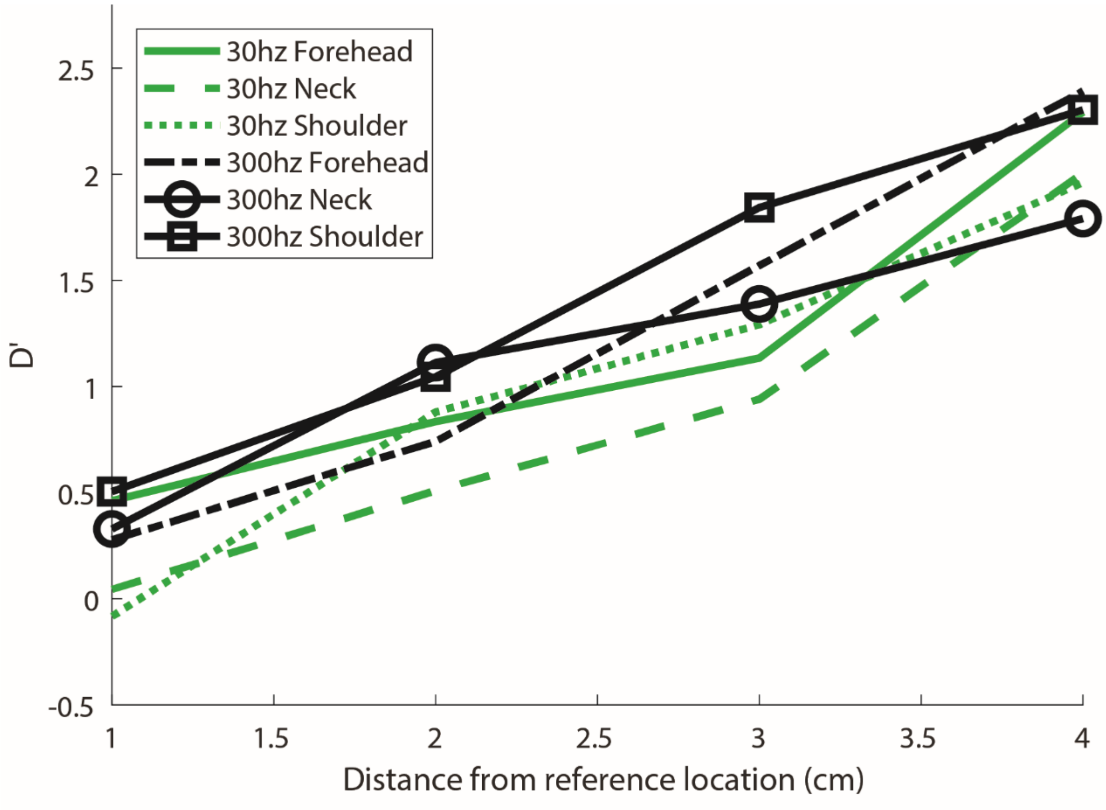

Figure 16 - Sensitivities (D') of downward movements at different distances, stimulation frequencies, and stimulation electrode configuration.

s

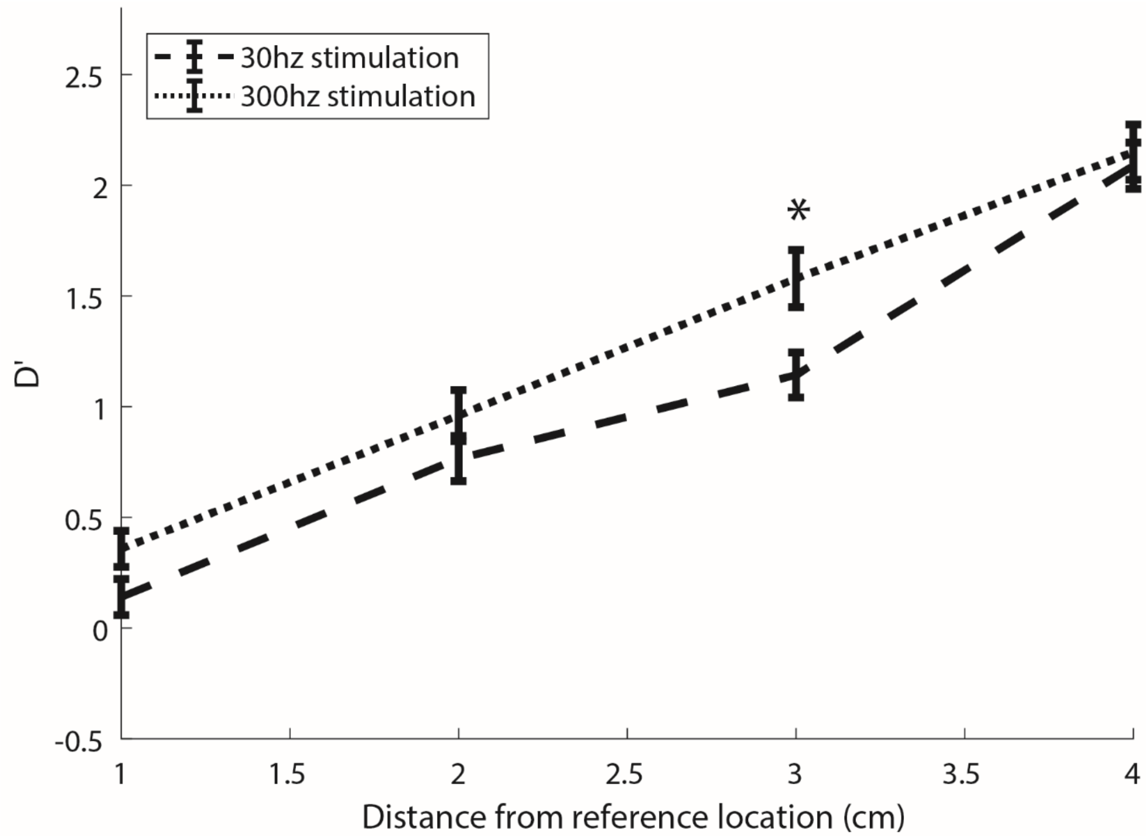

Figure 17 – Sensitivities (D') of downward movements at different distances and stimulation frequencies stimulation location collapsed.

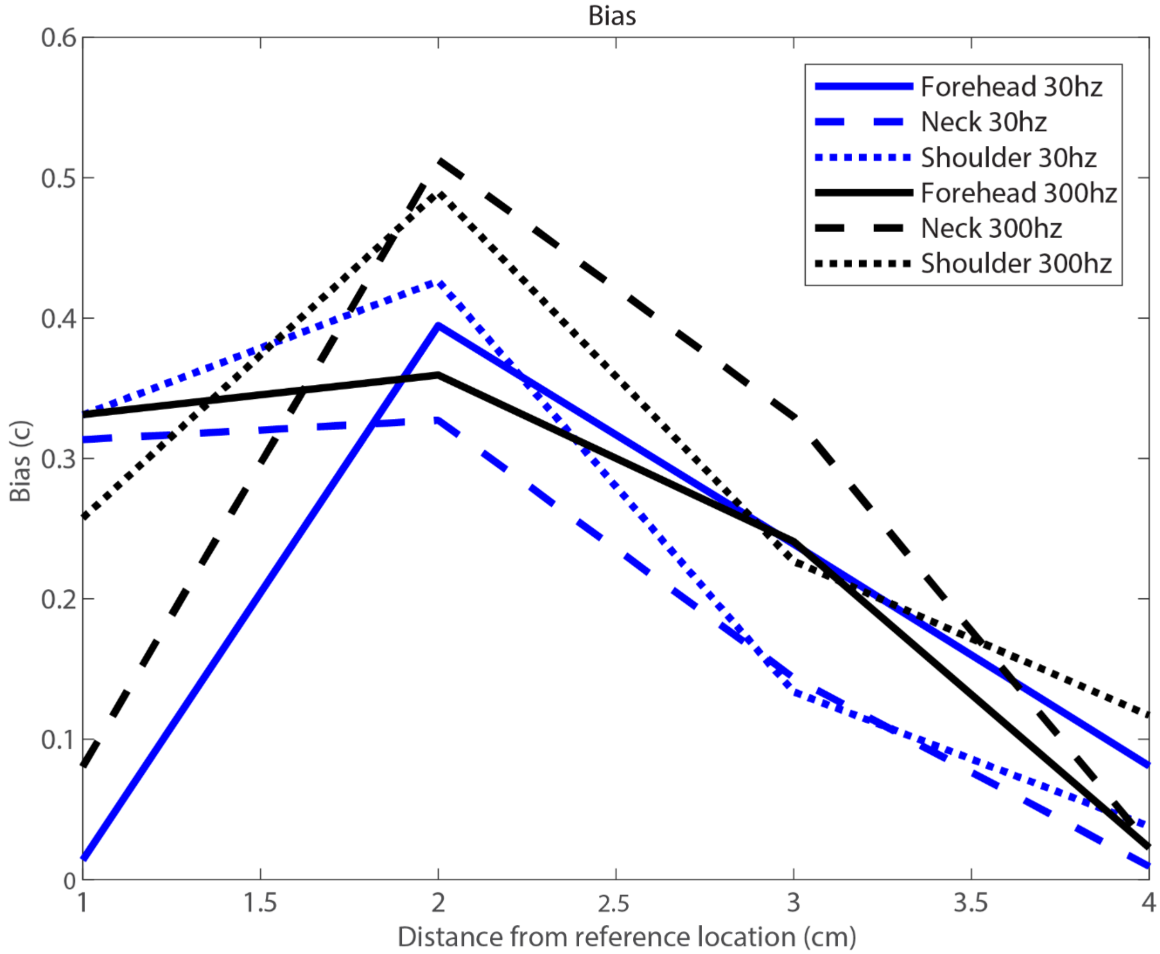

Figure 18 – Bias for all electrode configurations and stimulation frequencies shown. Significant difference of distance was shown statistically.

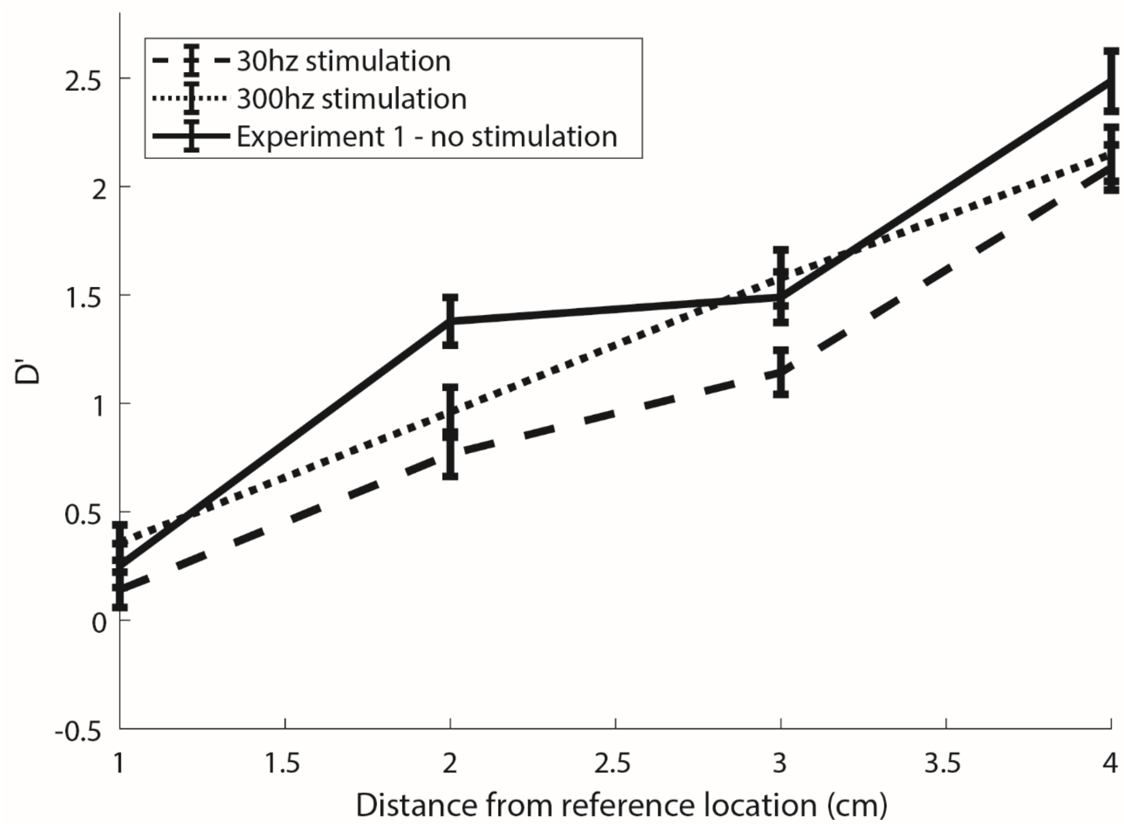

Figure 19 – Sensitivities (D') of downward movements at different distances and stimulation frequencies. Non-stimulation data presented from chapter 1 for visual comparison.

List of abbreviations

ADL – activity of daily living
AFC – Alternative Forced Choice
ARAS – Ascending Reticular Activating System
D' – ('dee-prime'). Unitless measure of sensitivity using hit rate and false alarm rates. Calculated as Z(hit rate) – Z(false alarm rate).
DoF – degrees of freedom
fA – false alarm rate
hR – hit rate
MS – Multiple Sclerosis
Pc – Percent correct
PD – Parkinson's Disease
SR – Stochastic Resonance
TDCS – Transcranial Direct Current Stimulation
TENS – Transcutaneous Electrical Nerve Stimulation
TNS – Trigeminal Nerve Stimulation
TMS – Transcutaneous Magnetic Stimulation
US - Ultrasound
VNS – Vagus Nerve Stimulation
Z(x) – z transform

CHAPTER 7 BIBLIOGRAPHY

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CHAPTER 8 APPENDIX A

PERMISSION FROM SCIENTIFIC JOURNAL

Chapter 3 is adapted from a published article in *Frontiers of Human Neuroscience*. It has been updated to change some language for readability, but previous results and conclusions have not been materially changed from their published form.

Klein, J., Whitsell, B., Artemiadis, P. K., & Buneo, C. A. (2018). Perception of Arm Position in Three-Dimensional Space. Frontiers in Human Neuroscience, 12. https://doi.org/10.3389/fnhum.2018.00331

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