MULTISENSORY INTEGRATION OF LOWER-LIMB SOMATOSENSORY NEUROPROSTHESES: FROM PSYCHOPHYSICS TO FUNCTIONALITY

by

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Submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

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CASE WESTERN RESERVE UNIVERSITY

January 2020

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Abbreviations

- A/P: anterior-posterior
- AKA: above-knee amputee
- BKA: below-knee amputee
- C-FINE: composite flat interface nerve electrode
- CoG: center-of-gravity
- CoP: center-of-pressure
- CPG: central pattern generator
- DBC: dynamic balance control
- EEG: electroencephalography
- ESAR: energy-storage-and-return
- FAI: fast/rapidly adapting I mechanoreceptor (Meissner's corpuscles)
- FAII: fast/rapidly adapting II mechanoreceptor (Pacinian corpuscles)
- FINE: flat interface nerve electrode
- fMRI: functional magnetic resonance imaging
- FSR: force-sensitive resistor
- IPI: inter-pulse interval
- JND: just noticeable difference
- LLA: lower-limb amputee
- LOS: limits of stability
- M/L: medial-lateral
- PNS: peripheral nerve stimulation
- PSS: point of subjective simultaneity
- PA: pulse amplitude
- PEEK: polyether ether ketone
- PW: pulse width
- RAI: fast/rapidly adapting I mechanoreceptor (Meissner's corpuscles)
- RAII: fast/rapidly adapting II mechanoreceptor (Pacinian corpuscles)
- RMLMM: repeated measures linear mixed model
- ROI: region of interest
- RSD: residual standard deviation
- RWS: rhythmic weight shift
- SI: primary somatosensory cortex
- SAI: slowly adapting I mechanoreceptor (Merkel's disk)
- SAII: slowly adapting II mechanoreceptor (Ruffini endings)
- SACH: solid-ankle-cushioned-heel
- SJ: simultaneity judgment
- SOA: stimulus onset asynchrony
- SOF: sense of feel
- TFA: trans-femoral amputee
- TIME: transversal intrafascicular multichannel electrode
- TTA: trans-tibial amputee
- ULA: upper-limb amputee

Acknowledgements

I have many people to thank for their support over the last several years… First, the research participants and their families who have selflessly volunteered many hours of their time. When I first started to work with human participants, I expected it to be something like a doctor-patient relationship. But when you spend several hours a week with someone, you get to know them quite deeply. They have become my Cleveland family, and it's a blessing I never expected. I am very thankful for them and I couldn't have asked for better people to spend my weeks with.

Next, I would like to express my deepest gratitude to thank my family. In many times of frustration and stress, they picked me up and dusted me off. My dad is my role model, and has always pushed me to accomplish more than I ever thought I could. He moved me across the country- twice! He was diagnosed with cancer when I was ten years old, and the doctors did not expect him to live to see me graduate high school. Now he's seeing me get my PhD, which makes it all the more special. Then there's my mom, who gives me regular pep talks and confidence boosts, often when I didn't know that I needed them. She always checks on me and makes sure I have a life outside of work, too. My brother, Sean, grew from a high school senior to an engineer at General Motors during my time at Case. He has always made an effort to spend time with me when I visit, which I know wasn't easy with his college schedule. Next, there's my brother Buzzie, who has Tuberous Sclerosis and functions at the level of an elementary schooler. He brightens up my life like I could never begin to explain. He is by far the most popular member of our family, and he makes me laugh and forget about any stress I'm facing. And finally, I have

to thank my little fur balls and all of my foster kittens who have given me endless cuddles and laughter.

And then there's my fiancé, Chass, who for some reason still wants to be with me after witnessing the chaos that is grad school. It takes a pretty special person who is willing to date someone that sometimes steals toilet paper from the gym but is nearly 30 years old. I'm so glad he stalked me on LinkedIn and didn't realize what he had gotten himself into. He makes me laugh, he listens to me vent, and he's always there for me to lean on. His dedication to his own career continuously inspires me to be better, and I love bragging about him. I can't wait for many more adventures.

Hamid, I cannot begin to my express my gratitude to you. Where would I be without you??? You taught me just about everything. You always encouraged me to grow and ask questions, without ever being condescending. I'm thankful that we have become close friends throughout all of it. I would like it officially documented here that I firmly believe you watch the Bachelor, despite what you tell me.

There are so many more people at Case that I am thankful for, but I want to highlight a couple of people in particular. Emily, you have always reminded about the importance of small details and having a strong understanding of how things work. I am so glad that we have become close friends (and llama twins) over the years! Julie, when I first moved here, you immediately welcomed me and helped ensure that Cleveland became home. I also want to give shout outs to Melissa, Ivana, and Liz, who I have shared many fun and emotional moments with. I am so proud to know such strong, intelligent, fun, and kind of weird women!

Finally, I would like to thank my guidance committee members Dr. Ronald Triolo, Dr. Dustin Tyler, Dr. Bolu Ajiboye, and Dr. Cenk Cavusoglu. I have really appreciated your helpful questions, comments, and suggestions in developing my research. Drs. Tyler and Triolo, I am extremely grateful that you both welcomed me to Case (twice!) and only tease me occasionally for picking ASU first. I greatly appreciate all of your shared wisdom and support over the years. Dr. Tyler, thank you for brainstorming with me and encouraging me to always think big. Dr. Triolo, one day, I hope to understand even a fraction of your television and movie references. You always made time for me and ensured that I could continue reaching my goals and creating new ones.

This work was supported in part by the DARPA BTO under the auspices of Dr. Al Emondi through the Space and Naval Warfare Systems Center, Pacific Contract No. N66001-15-C-4038. Funding was also provided by an NIH T32 grant #5T32EB004314-17. The Cleveland VA Medical Center provided facilities and additional resources.

Multisensory Integration of Lower-Limb Somatosensory Neuroprostheses:

from Psychophysics to Functionality

Abstract

by

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Over one million individuals in the United States have a lower-limb amputation. Though locomotion is a sensorimotor process, no commercially available prostheses offer somatosensory feedback, and amputees continue to face locomotor challenges. Recent studies have demonstrated that electrically stimulating the residual nerves of amputees can elicit somatosensory percepts referred to the missing limb.

Though peripheral nerve stimulation (PNS) takes advantage of the existing neural pathways that carry sensory information from the amputated limb to the brain, neural stimulation does not activate these afferent fibers in the same manner as physically-applied tactile stimuli. We hypothesized that these differences in neural activation may cause PNS-evoked sensation to be perceived differently than natural touch with respect to temporal synchrony and multisensory integration. In Aim 1, we found that the processing time and temporal sensitivity were not different between PNS-evoked and natural somatosensation. The similarity in visuotactile synchrony provided further evidence that PNS-evoked sensations are processed in broadly the same way as natural touch. In Aim 2, we established that much like natural somatosensation, vision and postural manipulations could reinforce PNS-evoked somatosensation. This multisensory integration had not been previously demonstrated and it is important for sensory

neuroprostheses, which will be used in diverse environments with various sensory resources.

The findings from Aims 1-2 demonstrated that PNS-evoked and natural somatosensation have similar properties, but did not guarantee that the body would utilize the sensory information accordingly. In Aim 3, we showed that amputees utilized PNS-evoked plantar sensation while performing a challenging locomotor task, revealing a significant and immediate benefit of somatosensory feedback to amputees. The use of a sensory-enabled prosthesis did not change the amputees' locomotor strategies, which indicated that longer-term therapeutic benefits might require a longer familiarization period with the device.

PNS allowed us to decouple sensory stimuli in a way that is not ordinarily possible, enabling probing of the underlying characteristics of multisensory integration. This dissertation lays the groundwork for future studies with additional target populations. Both trans-femoral and bilateral amputees are missing more sensory resources than unilateral trans-tibial amputees, and could benefit substantially from restoring balance resources, such as somatosensation.

Chapter 1: Background information

Lower-limb amputee population

Approximately 1.6 million people are living with an upper- or lower-limb amputation in the United States (Ziegler-Graham, MacKenzie, Ephraim, Travison, & Brookmeyer, 2008). One million individuals have a lower-limb amputation, 32% of which are minor amputations at the toe level (Timothy R. Dillingham, Pezzin, & MacKenzie, 2002). Approximately 28% occur at the trans-tibial level and 26% are trans-femoral, both of which require assistive devices such as a prosthesis or wheelchair. The remaining incident rates, from highest to lowest, correspond to foot, ankle, through-knee, hip disarticulation, pelvis, and bilateral amputations. Most major lower-limb amputations are due to vascular disease, such as diabetes and peripheral arterial disease (81%), and the remaining are caused by trauma (17%) and cancer (2%) (Ziegler-Graham et al., 2008).

Over 84% of lower-limb amputees regularly use a prosthesis (Timothy R. Dillingham, Pezzin, MacKenzie, & Burgess, 2001; Gailey et al., 2010; Raichle et al., 2008). Higher rates of prosthesis use are associated with younger age, employment, marriage, distal amputation, an amputation of traumatic etiology, and an absence of phantom limb pain (Raichle et al., 2008). Despite this widespread use, only 61% of lower-limb amputees are satisfied with the ease of use of their prostheses (T R Dillingham, Pezzin, MacKenzie, & Burgess, 2001). Coincidentally, lower-limb amputees report a lower quality of life than the general population (Sinha, Van Den Heuvel, & Arokiasamy, 2011). One of the most common complaints is limited locomotor functionality, making tasks such as navigating stairs without handrails or walking over uneven terrain challenging (Gauthier-Gagnon, Grisé, & Potvin, 1999).

One approach to improving amputees' quality of life is to improve prosthetic functionality. Our goal is to advance lower-limb prosthetic technology by adding somatosensory feedback via electrical stimulation of the nerves remaining in the residual limb. Prior work has shown that the addition of sensory feedback into a prosthesis can improve functional ability (Clark et al., 2014; Dhillon & Horch, 2005; Hebert et al., 2014; Horch, Meek, Taylor, & Hutchinson, 2011; Petrini et al., 2019; Pylatiuk, Kargov, & Schulz, 2006; Stanisa Raspopovic et al., 2014; Rusaw, Hagberg, Nolan, & Ramstrand, 2012; J. A. Sabolich, Ortega, & IV, 2002; Schiefer, Tan, Sidek, & Tyler, 2016; Tan et al., 2014), reduce phantom pain (Dietrich et al., 2012; Petrini et al., 2019; Tan et al., 2014), and enhance prosthesis embodiment (the incorporation of a prosthesis into one's body schema) (Arzy, Thut, Mohr, Michel, & Blanke, 2006; Emily L Graczyk, Resnik, Schiefer, Schmitt, & Tyler, 2018; Marasco, Kim, Colgate, Peshkin, & Kuiken, 2011; Mulvey, Fawkner, Radford, & Johnson, 2012; Schiefer et al., 2016).

Because the focus of this dissertation is on restoring sensation to trans-tibial amputees (TTAs), commonly referred to as below-knee amputees (BKAs), the remainder of the background chapter will focus on issues relevant to that segment of the amputee population. Some issues may also be relevant to trans-femoral amputees (TFAs), commonly referred to as above-knee amputees (AKAs), who require both a prosthetic foot and knee and could benefit from improvements to prosthetic feet. The information that follows, though, addresses only how they apply to BKAs and their relevance to a nerve-based approach to restoring natural sensation of foot-floor contact and ankle loading.

Existing prosthetic technologies for below-knee amputees

When developing a mechanism of sensory feedback, it is crucial to make it compatible with a wide range of prosthetic devices. Several types of suspension systems and below-knee prostheses are commercially available. The most common types of suspension systems are shuttle lock, vacuum, and suction suspension ("Keeping your leg on (suspension)," n.d.). With shuttle lock suspension, amputees roll a liner onto the residual limb. The liner contains a pin at the end that they insert into the socket, which has a shuttle lock built into the bottom. With vacuum and suction suspensions, amputees wear a sleeve on their residual limb that creates an airtight seal. These sleeves are typically made out of an elastic material. With vacuum suspension, as the individual stands up, air is expelled from the prosthetic socket. A vacuum effect holds the residual limb in place by utilizing the force of negative air pressure. With suction suspension, amputees insert the liner-covered residual limb into the socket and stand up, which expels excess air through a valve.

Skin irritation and wounds are commonly reported problems by lower-limb amputees (T R Dillingham et al., 2001). High pressure exerted by the prosthesis socket can cause pressure ulcers (Seelen, Anemaat, Janssen, & Deckers, 2003), and this risk is further increased if an amputee has age-related skin/tissue atrophy, polyneuropathy, vascular disorders, or oedema (Seelen et al., 2003). To minimize this risk, careful consideration is given to obtain a prosthesis that is properly sized and aligned. However, only 43% of lower-limb amputees are satisfied with prosthesis comfort (Timothy R. Dillingham et al., 2001), therefore new developments are underway to develop more classes of suspension systems. For example, an approach called osseointegration allows the prosthesis to be anchored to the bone of the residual limb (Brånemark et al., 2014; Hagberg, Kerstin; Brånemark, 2009).

Suspension systems and types of prosthetic limbs are independent. There are currently three primary types of prostheses for below-knee amputees: passive, semi-active, and active/powered prostheses (**Figure 1**). Passive prostheses do not have any electronic or mechanically moving parts. The two most common passive prostheses are solid-ankle-cushioned-heel (SACH) and energy-storage-and-return (ESAR). The SACH prosthesis has a foam rubber cushioned heel and wooden keel (the inner core) (Staros, 1957). ESAR prostheses store and release elastic energy during the gait cycle, typically through carbon fiber components that act as springs (Hafner, Sanders, & Czerniecki, 2002; Lemoyne, 2015). While walking, these components absorb energy during heel-strike and early-stance and return it during mid- to late-stance as propulsion. Previous studies comparing SACH and ESAR prostheses, which are both passive, have found few differences between stride length, cadence, muscle activity, energy expenditure, self-selected walking speed, and gait symmetry (see Hafner *et al.* 2002 for a comprehensive review) (Barth, Schumacher, & Thomas, 1992; Grabowski, Rifkin, & Kram, 2010; Hafner, Brian J; Sanders, Joan E; Czerniecki, Joseph M; Fergason, 2002; Hsu, Nielsen, Lin-Chan, & Shurr, 2006; Torburn, L; Perry, J; Ayyappa, E; Shanfield, 1990).

Figure 1: Examples of commercially available below-knee prostheses.

(a) The Vari-Flex foot (Össur EHF, Reykjavik, Iceland) is an example of a conventional, commercially energy-storage-and-return (ESAR) prosthesis (Childers & Takahashi, 2018). This passive prosthesis is constructed out of carbon fiber, titanium, and aluminum. Image courtesy Össur, Inc. **(b)** The élan foot (Blatchford Group, Hampshire, United Kingdom) is an example of a semi-active prosthesis. It adapts hydraulic resistance levels to modify prosthetic ankle angle. Printed with permission from Blatchford Inc. **(c)** The Empower® (Ottobock, Duderstadt, Germany) is an example of a commercially available active prosthesis. The Empower generates powered plantarflexion through battery-powered series-elastic actuators. Printed with permission from Ottobock.

Prostheses with semi-active damping can react to applied forces by changing their mechanical properties to better suit the activity being performed, but do not usually generate active forces. Typically, such devices can modify ankle angle by modifying their energy dissipation properties, for example by adjusting the stiffness of a spring (Jiménez-Fabián & Verlinden, 2012). The élan foot (Blatchford Group, Hampshire, United Kingdom) is a commercially available microprocessor-controlled foot that adapts hydraulic resistance levels to modify prosthetic ankle angle (**Figure 1**b).

Active/powered prostheses utilize pneumatics (Klute, Czerniecki, & Hannaford, 2002; Versluys et al., 2009), springs (Hitt, Sugar, Holgate, & Bellman, 2010), and/or motors (Au et al., 2008; Herr & Grabowski, 2012) to actively change ankle angle and generate power during plantarflexion (Lemoyne, 2015). The restoration of plantarflexion is intended to more closely mimic the physiologic power and range of motion of a healthy ankle. One commercially available powered prosthesis, the PowerFoot BiOM® (now called the Empower by Ottobock in Duderstadt, Germany) (Au et al., 2008; Herr & Grabowski, 2012), generates powered plantarflexion through battery-powered series-elastic actuators (**Figure 1**c). The actuators control ankle stiffness and power delivery using a state-based approach that matches built-in sensor data to a specific phase of gait. The BiOM is similar in size and weight to an intact ankle and foot, and can produce similar ankle power (Herr & Grabowski, 2012). No commercially available prostheses generate powered dorsiflexion, inversion, or eversion.

Finally, though myoelectric upper-limb prostheses have widespread use, there are no commercially available myoelectric lower-limb prostheses. Only recent studies have controlled ankle angle using continuous, proportional electromyography (EMG) control rather than state-based control (Fleming & Huang, 2019; Huang, Wensman, & Ferris, 2016; Kannape & Herr, 2014; Wang, Kannape, & Herr, 2013). The difficulty in transitioning these devices to the market is in part caused by sensor limitations and signal processing latency. EMG sensors must minimize large motion artifacts due to residual limb-socket dynamics during walking, and latency must be essentially non-existent. For upper-limb prosthesis users, delays greater than 125 ms between a motor command and prosthesis movement hinder task performance (Farrell & Weir, 2007), but delays are not typically unsafe. For lower-limb amputees, however, latency could compromise balance and increase fall risk. Additionally, it could further decrease gait speed, making such devices less desirable to potential users.

There is not a single prosthesis that is universally best for all below-knee amputees. Because our goal is to add sensory feedback to lower-limb prostheses, our system must be compatible with any type of below-knee prosthesis. This compatibility will assist the translation of the technology to other populations, such as above-knee amputees.

Functional challenges for below-knee amputees

Though there are many different classes of prostheses to choose from, some of which are quite sophisticated and technologically advanced, below-knee amputees still face functional challenges in everyday situations. Some of the most prevalent difficulties are outlined in the following subsections. This review is a critical step for formulating need statements and determining if sensory-enabled prostheses could be beneficial for lower-limb amputees.

Static standing

Prior studies are conflicting about whether unilateral below-knee amputees exhibit greater postural sway than able-bodied individuals while standing on a hard, stationary surface. In some studies, postural sway, as measured by center-of-pressure (CoP) variability, is greater for BKAs when standing either with the eyes open or the eyes closed (Buckley, O'Driscoll, & Bennett, 2002; Fernie & Holliday, 1978; A. C. Geurts, Mulder, Nienhuis, & Rijken, 1991; Hermodsson, Persson, Ekdahl, & Roxendal, 1994;

Isakov, Mizrahi, Ring, Susak, & Hakim, 1992). This is significant because increased CoP variability has been linked to future falls (Norris, Marsh, Smith, Kohut, & Miller, 2005).

In other studies, the postural sway during static standing was near normal during eyes open and eyes closed conditions (Howard, Perry, Chow, Wallace, & Stokic, 2017; Mohieldin, Chidambaram, Sabapathivinayagam, & Al Busairi, 2010; Vanicek, Strike, McNaughton, & Polman, 2009). Prior studies may be conflicting due to the presence of comorbidities, the age of the participants studied, cause of amputation, and/or small sample sizes. Nevertheless, it is reasonable to assume that some of the CoP variability observed may be due to lack of plantar pressure sensation and status of the ankle angle (Billot, Handrigan, Simoneau, Corbeil, & Teasdale, 2013; Hong, Manor, & Li, 2007).

Level ground walking

While walking over level ground, BKAs typically have a shorter stance duration on the prosthetic leg than the intact limb, leading to an asymmetrical gait (Isakov, Keren, & Benjuya, 2000). Most amputees also have a slower self-selected walking speed than able-bodied individuals (Herr & Grabowski, 2012; Paysant et al., 2006; Russell Esposito, Rodriguez, Ràbago, & Wilken, 2014). Below-knee prostheses cannot provide the same forward trunk propulsion and leg swing initiation as an intact leg (Zmitrewicz, Neptune, & Sasaki, 2007), largely due to their uniarticular function (Zmitrewicz et al., 2007). Because below-knee prostheses do not cross the knee joint, they are not mechanically similar to the biarticular gastrocnemius (a plantar flexor and knee flexor), which accelerates the leg forward to initiate swing. To compensate for this missing acceleration, activity of the rectus femoris (a knee extensor and hip flexor) increases to propel the trunk forward. This manifests in an increase in knee and hip power to achieve forward trunk propulsion. Consequently, BKAs have a 10–30% higher metabolic cost than non-amputees when walking at the same speed (Hsu et al., 2006; Paysant et al., 2006; Torburn, Powers, Guiterrez, & Perry, 1995; Robert L. Waters & Mulroy, 1999).

Compensatory actions at the hip and knee also ensure foot-floor clearance during swing (Sanderson & Martin, 1997). BKAs typically exhibit exaggerated hip and knee flexion on the amputated side during initial stance and swing phases of gait to functionally shorten the limb. This can be accompanied by circumduction or hip hiking to further ensure that the prosthetic foot clears the ground. Additionally, lower-limb prostheses are typically constructed to be shorter than the unaffected limb for the same purpose of toe clearance (Friberg, 1984). This asymmetrical loading on the body leads to chronic lower back, hip, and knee pain (Nolan et al., 2003; Norvell et al., 2005).

When BKAs wear a powered prosthesis during level ground walking, their metabolic costs, self-selected walking speeds, and step-to-step transition work are more comparable to non-amputees than when walking with a passive prosthesis (Esposito, Whitehead, & Wilken, 2016; Herr & Grabowski, 2012; Jeffers & Grabowski, 2017). However, gait is still asymmetric and peak hip power actually increases while wearing the BiOM, suggesting that plantar flexor power gets redistributed to hip flexors to facilitate leg swing (Ferris, Aldridge, Rábago, & Wilken, 2012). During level ground gait with a proportional myoelectric powered prosthesis, improvements in compensatory actions have not yet been reported. However, short-term gait symmetry improved after undergoing split-belt treadmill training (Kannape & Herr, 2016). Training, prosthesis hardware design changes, and/or the addition of sensory feedback may be necessary to improve gait symmetry and minimize compensatory actions.

Uneven terrain

People with below-knee amputations differ most significantly from able-bodied individuals when walking on uneven terrain, stairs, and ramps. The presence of uneven terrain is linked to a higher frequency of falling for BKAs (Ülger, Topuz, Bayramlar, Erbahçeci, & Şener, 2010). When walking in untended and uneven grass (height ~1”), BKAs have a slower walking speed, shorter stride length, and a higher heart rate, oxygen uptake, oxygen cost, and ratings of perceived exertion than able-bodied individuals (Paysant et al., 2006). While walking over gravel, BKAs typically take shorter and wider steps and have more hip and knee flexion during the initial stance and swing phases compared to able-bodied individuals (Gates, Dingwell, Scott, Sinitski, & Wilken, 2012). These compensatory strategies are still present while wearing a powered prosthesis (Gates, Aldridge, & Wilken, 2013), and the impact of proportional myoelectric powered prostheses has not yet been studied. Though BKAs can navigate over uneven terrain, it is challenging. Receiving feedback of ankle angle and contact pressures on different regions of the foot could alleviate these difficulties and boost balance confidence.

Stairs

During stair ascent and descent, BKAs typically walk at a slower speed than able-bodied individuals and increase their step width (Powers, Boyd, Torburn, & Perry, 1997; Ramstrand & Nilsson, 2009). They also demonstrate stance asymmetry between the prosthetic and intact limbs, tending to spend more time on the intact limb (Powers et al., 1997). Just as with gait over level-ground or uneven terrain, BKAs adopt compensatory hip and knee strategies that result in greater muscular effort (measured by electromyography). Compared to able-bodied individuals, below-knee amputees have greater hip flexion during the stance phases of stair ascent and descent, and also have less knee flexion during the stance phase of stair descent. When ascending stairs with a powered prosthesis, the ankle range of motion and power improved, but BKAs still adopted a compensatory hip strategy, consisting of greater affected limb hip flexion during stance (Aldridge, Sturdy, & Wilken, 2012). The compensatory strategies and gait symmetry of below-knee amputees while navigating stairs with proportional myoelectric powered prostheses have not yet been studied. In particular, slow walking speed while navigating stairs may be due to lack of plantar pressure sensation that confirms when the prosthesis makes contact with the ground.

Ramps

Compared to age-matched controls, BKAs walk at a slower speeds when ascending or descending a 5° incline (Vickers, Palk, McIntosh, & Beatty, 2008). They also exhibit decreased knee and hip range of motion, hip moments, and vertical ground reaction forces. The asymmetrical gait reported with level-ground walking, uneven terrain, and stairs also occurs with ramps; BKAs spend less time on the prosthetic limb than the intact limb while walking up or down an inclined surface. When traversing ramps with a powered prostheses, BKAs exhibit larger positive work and net work than while wearing passive prostheses (Jeffers & Grabowski, 2017). This leads to improved symmetry between the legs, which has been directly linked to metabolic cost (S. J. Mattes, Martin, & Royer, 2000). The compensatory strategies and gait symmetry of below-knee amputees while navigating ramps with proportional myoelectric powered prostheses have not yet been studied. The combination of semi-active or powered prostheses with sensory feedback may be necessary to further improve gait symmetry.

Response to perturbations

The functional limitations and compensatory strategies of BKAs are relatively similar between different gait scenarios (walking over level ground, uneven terrain, stairs, and ramps). In response to perturbations, able-bodied people employ movements at the ankle or hip. They adopt an "ankle strategy" to react to low frequency perturbations and a "hip strategy" in response to larger perturbations (Fay B. Horak, Shupert, & Mirka, 1989; Winter, 1995). Unilateral lower-limb amputees do not have active ankle control in both feet, and therefore cannot react to balance disturbances in this manner. To better understand amputees' response to perturbations, below-knee amputees were asked to maintain their balance without moving their feet during random, continuous platform movements in the sagittal plane (Nederhand, Van Asseldonk, Der Kooij, & Rietman, 2012). Indices of stability were recorded, including weight distribution and a measure called dynamic balance control (DBC), which incorporated center-of-pressure and foot and ankle position. Although it was not statistically significant, all BKAs showed weight-bearing asymmetry, placing just 42$\pm$4% of body weight on the affected limb during perturbations. The DBC was significantly different between amputees and able-bodied individuals, meaning that the contribution of both legs to balance control was more asymmetrical for unilateral lower-limb amputees. Shifting weight away from the prosthetic limb and increasing dependence on the intact limb can be largely explained by a lack of sensory feedback (Nurse & Nigg, 2001).

Over-dependence of BKAs on remaining postural resources

All individuals utilize a “postural reserve” of resources to maintain balance. This resource pool consists of vision, the vestibular system, cognitive attention, somatosensory inputs, and the musculoskeletal system (Lacour, Bernard-Demanze, & Dumitrescu, 2008; M. Woollacott & Shumway-Cook, 2002). All sensory information must be integrated in order to interpret and respond to the surrounding environment. When any postural resources are perturbed or eliminated, compensatory sensory reweighting occurs. Senses with the least amount of noise/uncertainty and the highest importance to achieving a task are weighted the highest (Ernst & Banks, 2002; Fay B. Horak, 2006; Van Der Kooij & Peterka, 2011). During locomotion, sensory reweighting helps lower-limb amputees maintain their balance.

To assess how an individual weights each sense, one or more resources can be perturbed while the individual is instructed to maintain balance. Visual contributions can be evaluated by asking individuals to close their eyes. Vestibular information can be perturbed by moving visual surroundings while an individual keeps his or her head stationary. Cognitive dependence is typically studied using a dual-task paradigm, which combines a balance task with a cognitive task. Balance tasks typically consist of gait, static standing, or standing on a moving platform. A few common cognitive tasks include the Stroop test (Stroop, 1935), mental math, spelling five-letter words backwards, and a verbal fluency task (listing words starting with a specific letter, (Borkowski, Benton, & Spreen, 1967)). Somatosensory information (tactile and proprioception) can be disrupted by translating or rotating the support surface, or by making the surface more compliant, such as by standing on a piece of foam (MacLellan & Patla, 2006). This instability of the supporting surface causes somatosensory information to be compromised; tactile inputs from contact with the support surface are altered in unexpected ways (Pasma, Boonstra, Campfens, Schouten, & Van der Kooij, 2012), or proprioceptive inputs are removed and lower-limb muscle lengths change unpredictably with respect to changes in body orientation (Kiers, Brumagne, Van Dieën, Van Der Wees, & Vanhees, 2012; Lewis M. Nashner, 1982).

The sensory organization test (SOT) assesses an individual's dependence on vision, vestibular information, and somatosensation by perturbing one or more variables at a time (L. M. Nashner & Peters, 1990). An equilibrium score is calculated for each condition comparing the mean anterior/posterior center-of-gravity (A/P CoG) excursion against a maximal stability limit of 12.5° body sway. Dependence on one sensory resource is calculated by dividing the equilibrium score of the condition with the most dependence on that resource by the baseline equilibrium score (static standing with the eyes open) (Barnett, Vanicek, & Polman, 2013). For instance, when an individual is standing on a moving platform with their eyes closed, somatosensory and visual information are both compromised and the individual must rely on vestibular information to maintain balance (Equation 2).

$$\textbf{Dependence on visual inputs} = \frac{Equilibrium\ score\ of\ SOT\ condition\ 4\ (moving\ platform, eyes\ open)}{Equilibrium\ score\ of\ SOT\ condition\ 1\ (stable\ platform, eyes\ open)}$$

Equation 1

$$\textbf{Dependence on vestibular inputs} = \frac{Equilibrium\ score\ of\ SOT\ condition\ 5\ (moving\ platform, eyes\ closed)}{Equilibrium\ score\ of\ SOT\ condition\ 1\ (stable\ platform, eyes\ open)}$$

Equation 2

$$\textbf{Dependence on somatosensory inputs} = \frac{Equilibrium\ score\ of\ SOT\ condition\ 2\ (stable\ platform, eyes\ closed)}{Equilibrium\ score\ of\ SOT\ condition\ 1\ (stable\ platform, eyes\ open)}$$

Equation 3

While standing on a firm and flat surface in a well-lit environment, able-bodied individuals typically prioritize somatosensation the most (70%), then vestibular information (20%), and then vision (10%) (Peterka, 2002). On an unstable surface, when somatosensory information becomes unreliable, sensory reweighting changes to prioritize vestibular information (60%), vision (30%), then somatosensation (10%) (Peterka, 2002). By reweighting sensory information to utilize remaining resources, able-bodied individuals can maintain balance.

Unilateral lower-limb amputees are missing afferent information from receptors in the muscles, tendons, and skin; therefore, they lack somatosensory and musculoskeletal feedback from the missing limb. When a prosthesis is adequately fitted, an amputee can incorporate pressures from the socket/limb interaction as feedback regarding forces between the prosthesis and the ground (E. M. Burgess, Rappoport, & States., 1992). This pressure feedback is crude and attenuated, but BKAs compensate for minor threats to stability by utilizing it along with remaining somatosensory and musculoskeletal information and their visual, vestibular, and cognitive resources (A. C. Geurts, Mulder, Nienhuis, & Rijken, 1992).

Because of the remaining postural resources and sensory reweighting, it is difficult for the untrained eye to see any deficits of BKAs during simple tasks such as over-ground walking on a level surface. Deficits become more apparent in two situations: in long-term wear and tear of the body, and in scenarios that deplete remaining postural resources. Lower limb amputees primarily depend on their intact limb to maintain balance control during static and dynamic tasks, but they also heavily rely on visual information (Barnett et al., 2013; Buckley et al., 2002; Isakov, Mizrahi, Susak, Ona, & Hakim, 1994; Vanicek et al., 2009; Vrieling et al., 2008). Overuse of the intact limb has destructive long-term consequences, such as osteoarthritis of the intact knee and/or hip (Gailey, Allen, Castles, Kucharik, & Roeder, 2008). Decreased loading on the residual limb can also lead to osteopenia and subsequent osteoporosis. When unilateral BKAs perform a SOT, their balance is most unstable during static and dynamic standing conditions in which vision is eliminated (Jayakaran, Johnson, & Sullivan, 2015; Vanicek et al., 2009). This heavy reliance on vision by unilateral BKAs puts balance at risk when vision is compromised, such as at night, in busy crowds, or in unfamiliar environments.

It is anecdotally reported that amputees prefer prostheses that they perceive as less cognitively demanding (Hafner, Willingham, Buell, Allyn, & Smith, 2007; Williams et al., 2006), which is likely because they cannot spare that postural resource. When cognitive attention is compromised, amputees have less postural stability than able-bodied individuals (Howard, Perry, et al., 2017; Howard, Wallace, Abbas, & Stokic, 2017). During static standing, the postural sway of BKAs (measured by CoP variability) increases more than the sway of able-bodied individuals when a cognitive load is imposed (Howard, Perry, et al., 2017). Large values of postural sway are an indicator for future falls (Norris et al., 2005). In another study, BKAs walked over an electronic walkway while performing mental math or backwards spelling (Howard, Wallace, et al., 2017). A metric called residual standard deviation (RSD) was developed to quantify the variability in stride length and cadence during gait. When baseline walking and dual-task walking were compared, the RSD increased more for amputees than for able-bodied controls, meaning that their balance was more negatively impacted when cognitive load was imposed. This puts BKAs at risk for falls when attention is temporarily removed from their postural reserve, such as when they are crossing a busy street or talking to a friend.

During locomotion, sensory reweighting and dependence on remaining postural resources helps lower-limb amputees maintain their balance. Though fairly effective, it leads to decreased balance confidence and an overall fear of falling (Kulkarni, Wright, Toole, Morris, & Hirons, 1996; William C. Miller, Speechley, & Deathe, 2001). Adding resources such as somatosensory feedback into the postural reserve could significantly improve balance and quality of life.

Somatosensation in the healthy foot

When developing sensory-enabled below-knee prostheses, it is important to first consider the anatomy of the missing foot. Information about touch is transmitted from mechanoreceptors to the brain by myelinated Aα and Aβ afferent fibers. Aα fibers are typically 12-20 µm in diameter with conduction velocities between 72-120 m/s. Aβ fibers are approximately 6-12 µm in diameter with 36-72 m/s conduction velocities (Kandel, Schwartz, & Jessell, 2000) A cell in the skin that responds to physical deformation is referred to as a mechanoreceptor. Mechanically-gated ion channels in the membrane of a mechanoreceptor open and close in response to physical deformations. There are four classes of mechanoreceptors on the glabrous plantar surface of the foot: RAI, RAII, SAI, and SAII. SAI (slowly adapting type 1) and RAI (rapidly adapting type 1) mechanoreceptors are located in shallower layers of the skin, and SAII and RAII receptors are located in the deep dermis. SAI respond best to indentation, SAII to stretch, RAI to tapping and fluttering (low frequency vibrations), and RAII to high frequency vibrations.

Table 1: Distribution, force thresholds, and receptive field size of mechanoreceptors in the hand and foot

In the '*Distribution'* column, the percentage of each type of mechanoreceptor is given for both the hand and the foot. The next column contains the median amount of force needed to activate each type of mechanoreceptor in the hand and the foot. The receptive field area of each mechanoreceptor class is listed in the far right column.

	Distribution		***Force thresholds (median)***		***Receptive field size***	
	Hand (R. S. Johansson & Vallbo, 1979)	**Foot** (Strzalkowski, Peters, Inglis, & Bent, 2018)	**Hand** (R. S. Johansson, Vallbo, & Westling, 1980)	**Foot** (Kennedy & Inglis, 2002)	**Hand** (R. S. Johansson & Vallbo, 1980)	**Foot** (Kennedy & Inglis, 2002)
SAI	25%	18%	1.3 mN	35.6 mN	11 mm^2	71 mm^2
SAII	19%	21%	7.5 mN	115.3 mN	59 mm^2	127 mm^2
RAI	43%	48%	0.6 mN	11.8 mN	13 mm^2	38 mm^2
RAII	13%	13%	0.5 mN	4.0 mN	101 mm^2	284 mm^2

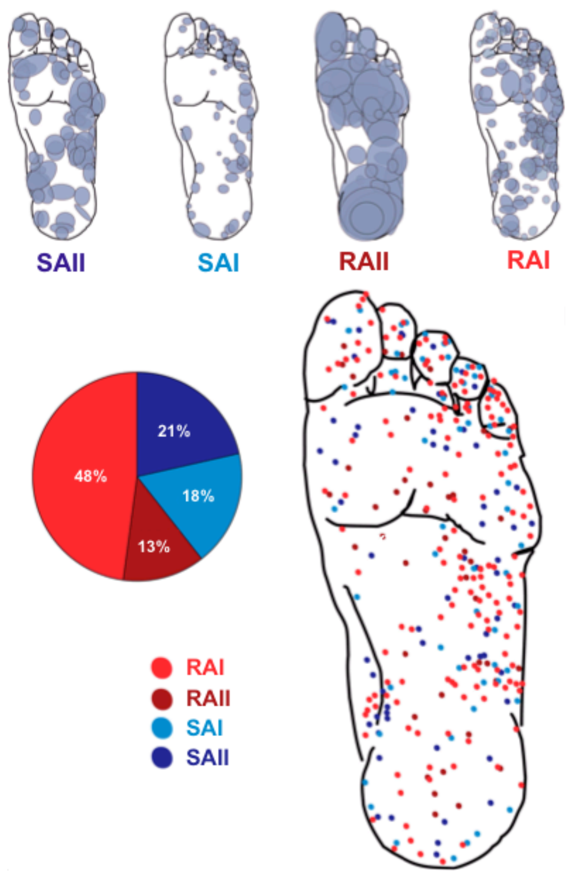
Table 2: Two-point discrimination and skin thickness of the hand and foot sole

The results of two-point discrimination tasks with the fingertip, palm, and foot sole are estimates that were extracted from a graph in a previous publication (Mancini et al., 2014). The skin thickness of the epidermis plus the dermis in the palm and foot sole is listed in the column on the far right (Y. Lee & Hwang, 2002).

	Two-point discrimination (mean)	***Skin thickness (mean $\pm$ standard deviation)***
Hand	Fingertip: 0.2 cm Palm: 0.75 cm	Palm: 1.35 ± 0.19 mm
Foot sole	1.4 cm	1.57 ± 0.58 mm

Figure 2: *Spatial distribution of mechanoreceptors in the foot.*

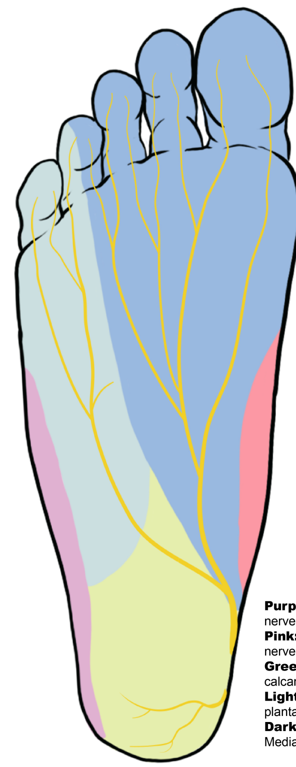
Mechanoreceptors in the plantar surface of the foot are clustered in the lateral midfoot, lateral metatarsals, and lateral toes. RAI mechanoreceptors, which respond to low frequency vibrations, make up the largest percentage of cells. Image courtesy of (Strzalkowski et al., 2018).



Mechanoreceptors are accumulated in the lateral midfoot, lateral metatarsals, and the lateral toes, which implies spatial differences in sensitivity (Strzalkowski et al., 2018) (**Figure 2**). An earlier study published that there is not a clear accumulation, however the sample size was too low to make clear estimates of afferent distribution and density (Kennedy & Inglis, 2002). Mechanoreceptor clustering is also seen in the hand, which has mechanoreceptors concentrated near the fingertips (R. S. Johansson & Vallbo, 1979). Approximately 61% of the mechanoreceptors in the foot are classified as “rapidly

Figure 3: *Sensory dermatomes in the foot sole.*

At the ankle, the tibial nerve divides into three branches: the calcaneal, medial plantar, and lateral plantar nerves. Branches of the tibial and common peroneal nerves also combine to form the sural nerve. The saphenous nerve is the terminal cutaneous branch of the femoral nerve. The regions of innervation of each nerve are shown below using different colors. Illustration courtesy of the APT Center at the Louis Stokes Cleveland VA Medical Center.



adapting” to sensory inputs. They respond best to vibration, tapping, and fluttering sensations. Force thresholds (Kennedy & Inglis, 2002) and receptive field size (R. S. Johansson & Vallbo, 1980; Kennedy & Inglis, 2002) are larger in the foot than in the hand (Table 1). The relative numbers of each type of mechanoreceptor in the hand and foot are not different (R. S. Johansson & Vallbo, 1979; Kennedy & Inglis, 2002; Strzalkowski et al., 2018). Two-point discrimination (Mancini et al., 2014) and skin thickness (Y. Lee & Hwang, 2002) are also larger in the foot than the hand (Table 2). Higher activation thresholds in the foot are likely attributed to thicker skin in that region (1.57$\pm$0.58 mm in the foot sole and 1.35$\pm$0.19 mm in the palm of the hand) (Kennedy & Inglis, 2002).

Mechanoreceptors in the plantar surface of the foot transmit information to the brain by the femoral and sciatic nerves. The femoral nerve is comprised of L2-L4 spinal nerves and the sciatic nerve is comprised of the L4-S3 spinal nerves. The saphenous nerve is the terminal cutaneous branch of the femoral nerve, and it innervates the posterior medial edge of the foot sole (**Figure 3**). At the popliteal fossa, the sciatic nerve splits into two branches: the common peroneal and tibial nerves. Cutaneous branches of the tibial and common peroneal nerves form the sural nerve, which innervates the lateral posterior edge of the foot sole. At the ankle, the tibial nerve divides into three branches: the calcaneal, medial plantar, and lateral plantar nerves. The medial calcaneal nerve innervates the heel. The medial and lateral plantar nerves innervate the remaining medial and lateral regions of the foot sole. During everyday tasks, such as navigating stairs and ramps, sensory information about one's environment is provided by the plantar surface of the foot, which is primarily innervated by the tibial nerve.

Why is sensation important in the lower-limb?

Plantar cutaneous sensation is an essential component of gait and balance because it provides feedback regarding interactions of the foot with the environment. Mechanoreceptors in the skin of the foot sole transduce spatial and temporal information about contact pressures (P. R. Burgess & Perl, 1973; Kennedy & Inglis, 2002). Afferent information from the plantar surface of the foot can be briefly eliminated using hypothermic anesthesia (Eils et al., 2004, 2002; McKeon & Hertel, 2007; Paillard, Bizid, & Dupui, 2007; Patel, Fransson, Johansson, & Magnusson, 2011; Perry, McIlroy, &

Maki, 2000; Schlee, Sterzing, & Milani, 2009). When plantar sensation is temporarily removed in both feet of able-bodied individuals, static standing, gait, and response to perturbations are negatively impacted. Postural sway, as measured by CoP variability, increases during static standing both with the eyes open (Billot et al., 2013; Hong et al., 2007) and eyes closed (Hong et al., 2007). During gait, spatiotemporal characteristics such as stance-phase duration, stride duration, and stride length are unchanged (Hohne, Ali, Stark, & Bruggemann, 2012). However, people adopt a more crouched posture while walking, characterized by increased knee flexion and ankle dorsiflexion during stance phase. When plantar sensation is eliminated in non-amputees, characteristics of balance and gait resemble those of below-knee amputees.

Moreover, when plantar sensation is temporarily eliminated, additional reactive steps are needed to restore equilibrium following perturbations administered by sudden and unexpected translation of the support surface in forward, backward, or lateral directions while standing (Perry et al., 2000). Increased postural sway and the need for multiple steps to recover balance are linked to increased fall risk (Luchies, Alexander, Schultz, & Ashton‐Miller, 1994; McIlroy & Maki, 1996; Norris et al., 2005; Wolfson, Whipple, Amerman, & Kleinberg, 1986). If cutaneous information is eliminated in one region of both feet (both forefeet or both rearfeet) of non-amputees via immersion in an ice bath, people shift their body weight away from the iced, insensate regions of the feet during gait (Nurse & Nigg, 2001). This is much like how unilateral lower-limb amputees shift more body weight onto their intact limb than their affected limb. Cutaneous plantar sensation plays a crucial role in maintaining balance and body posture during gait, and maintaining compensatory reactions to prevent falls (Do, Bussel, & Breniere, 1990).

As previously mentioned, walking with myoelectrically-controlled powered prostheses only improves gait after undergoing a training regime (Kannape & Herr, 2016). The need for training likely has to do with sensorimotor integration. When plantar cutaneous sensation is eliminated in just one foot, able-bodied individuals adopt a more cautious walking pattern: dorsiflexion is reduced at the beginning of the stance phase of gait, and plantarflexion is decreased during push-off (Eils et al., 2004). Even though the ankle still has the capacity to plantarflex and dorsiflex, it is not natural behavior without accompanying sensory feedback, and therefore requires training. It is well established that somatosensation and the motor system are not independent entities in able-bodied individuals (for a review, please see (Hatsopoulos & Suminski, 2011)). To improve motor control of a volitionally-controlled prosthetic ankle, information about cutaneous plantar sensation must be present.

Methods for adding sensory feedback to below-knee prostheses

Amputees can derive crude feedback regarding forces between the prosthesis and the ground from the distribution of pressures from the socket on their residual limbs, as previously noted (E. M. Burgess et al., 1992). More informative sensory feedback about foot-floor contact pressures can be delivered by auditory cues (Yang et al., 2012), vibration (Marayong et al., 2014; Rokhmanova & Rombokas, 2019; Rusaw et al., 2012; Wan, Wong, Ma, Zhang, & Lee, 2016), electrocutaneous sensation (Dietrich et al., 2018; J. A. Sabolich & Ortega, 1994), or electrical peripheral nerve stimulation (PNS) (Charkhkar et al., 2018; Clippinger, Seaber, McElhaney, Harrelson, & Maxwell, 1982).

Force sensors placed underneath the prosthesis typically trigger application of such sensory feedback signals. In some studies, the magnitude of a sensory stimulus is scaled to the magnitude of foot-floor contact pressure. Each sensory feedback method is described in more detail in the following sections.

Auditory cues

Auditory feedback can provide information about foot-floor contact. Real-time auditory cues based on stance time symmetry have been shown to help improve gait symmetry in unilateral BKAs (Yang et al., 2012). One benefit of this method is that it can be easily implemented. However, in environments that tend to have higher ambient noise, such as a shopping mall, it could be easy to miss an auditory cue. Conversely, in quiet public places such as the workplace, an auditory cue could attract attention or be distracting to others.

Vibration

Vibration applied to the skin can provide feedback regarding the center-of-pressure of the foot (Rusaw et al., 2012), knee angle (Marayong et al., 2014), and the location of objects underneath the prosthesis (Wan et al., 2016). Vibration can convey foot-floor information to the proximal residual leg (Rokhmanova & Rombokas, 2019; Rusaw et al., 2012) or even the hand (Wan et al., 2016). In one study, four vibrating tactors around the circumference of the thigh relayed information about forces applied to sensors underneath the prosthetic toes, first metatarsal, fifth metatarsal, and heel (**Figure**

4). It is also possible to propagate vibration to the residual limb by incorporating a vibrating motor into the pylon of a prosthesis (Marayong et al., 2014).

The benefits of vibratory feedback are that it is a non-invasive technique and poses a low safety risk. A drawback is that the stimulus modality (vibration) does not resemble typical contact between the foot and an object (pressure). Some amputees have reported that vibratory feedback feels distracting (Pylatiuk et al., 2006). Additionally, there is a learning curve for associating a substitutive sensory stimulus with an event. The learning curve is steepest when both the location and quality of the feedback do not match the event that triggers them.

Figure 4: *Depiction of a below-knee prosthesis with vibratory feedback by Rusaw et al.*

This vibratory feedback device was tested with 24 unilateral below-knee amputees (Rusaw et al., 2012). Four vibrating tactors around the circumference of the thigh relayed information about force applied to the prosthetic toes, first metatarsal, fifth metatarsal, and heel. Reprinted with permission from the Journal of Rehabilitation Research & Development (Rusaw et al., 2012).

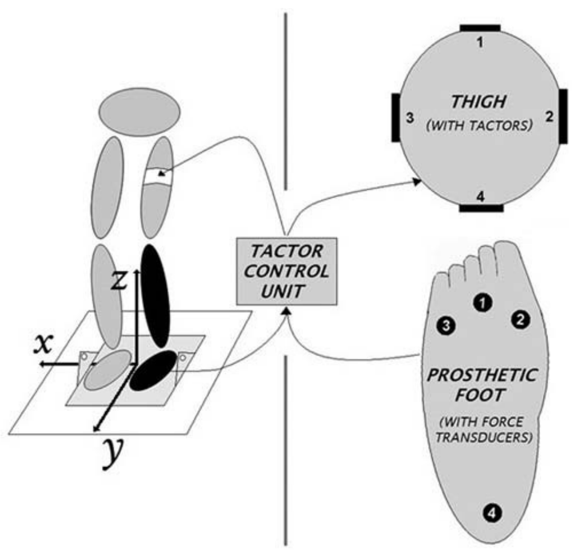
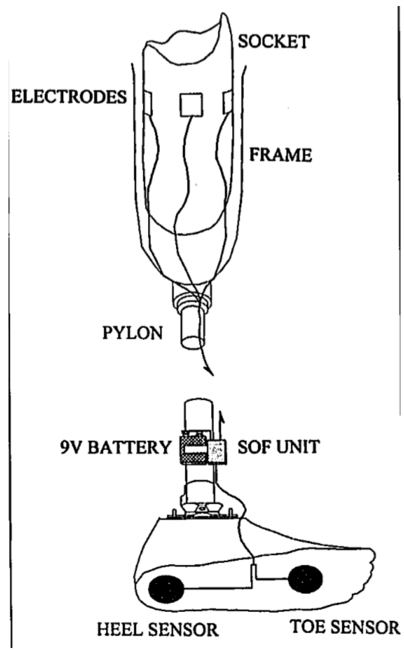


Figure 5: *Image of below-knee prosthesis with electrocutaneous sensory feedback by Sabolich & Ortega.*

The SOF (Sense-of-Feel) device setup was tested with 12 unilateral below-knee amputees (J. A. . Sabolich & Ortega, 1994). Electrodes were placed on the surface of the skin, underneath the prosthesis socket, to deliver transcutaneous electrical neural stimulation. Force applied to the toe sensor underneath the prosthesis resulted in stimulation applied to the anterior calf, and heel sensor activation resulted in stimulation applied to the posterior calf. Reprinted with permission from Wolters Kluwer Health, Inc. (J. A. . Sabolich & Ortega, 1994)



Electrocutaneous stimulation

Electrocutaneous stimulation (also called transcutaneous electrical stimulation) is another potential mechanism of sensory feedback. It is delivered by passing stimulating currents through electrodes located on a sensate region of the skin. Electrodes can be placed underneath the prosthesis socket (**Figure 5**) (J. A. . Sabolich & Ortega, 1994) or more proximally on the residual leg (Dietrich et al., 2018). In one study, electrocutaneous stimulation on the calf signified pressure applied to the prosthetic heel, and stimulation on the shin signified toe pressure (J. A. . Sabolich & Ortega, 1994). In another study, electrocutaneous stimulation of the thigh provided confirmation of contact between the ground and the prosthetic midfoot and forefoot (Dietrich et al., 2018). Similar to vibratory feedback, this technique is non-invasive but stimulus modality (typically paresthesia) does not resemble foot-object contact pressures. Additionally, discomfort or pain is often associated with electrocutaneous stimulation (Mason & Mackay, 1976).

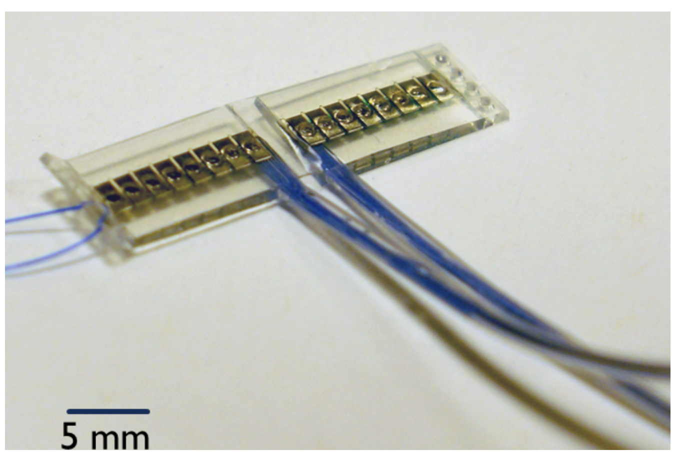
Peripheral nerve stimulation

After amputation, many lower-limb amputees have afferent neural fibers in the residual limb that remain intact and can transmit somatosensory information to the brain. Electrical stimulation can be applied directly to the residual peripheral nerves to evoke somatosensory percepts referred to the missing limb. Intraneural (Petrini et al., 2019) and extraneural (Charkhkar et al., 2018; Clippinger et al., 1982) electrodes can both evoke somatosensory percepts referred to the missing leg. Intraneural stimulation has been delivered to the residual tibial nerve of two above-knee amputees using transversal intrafascicular multichannel electrodes (TIMEs) (Petrini et al., 2019). The electrodes were implanted for three months. In response to stimulation, the participants reported feelings of touch, pressure, vibration, muscle activation, tingling, pulsation, and electricity referred to the missing foot sole and lower leg. Extraneural stimulation is less invasive than intraneural stimulation, as it does not puncture the epineurium. In a prior study, platinum-iridium electrodes were sutured to the sciatic nerve of 13 lower-limb amputees (Clippinger et al., 1982). That study stated that sensory feedback was achieved, but did not report the location or modality of evoked sensations, psychophysical properties, or percept stability over time. Up until recently, peripheral nerve stimulation for sensory-enabled prostheses had not been tested with below-knee amputees.

Our group has developed an extraneural stimulation method for delivering sensory feedback to below-knee amputees (Charkhkar et al., 2018). We have demonstrated that nerve cuff electrodes implanted around the distal sciatic, common peroneal, and tibial nerves can evoke somatosensory percepts referred to the missing feet of below-knee amputees. Our first target population was unilateral below-knee amputees for several reasons. They make up the largest percentage of lower-limb amputees (Timothy R. Dillingham et al., 2002) and their knee joints are intact. Also, the target nerves are preserved and closest to where the foot was. This makes them easier to activate with extraneural stimulation.

Figure 6: *Image of a 16-contact C-FINE.*

The composite flat interface nerve electrode (C-FINE) with 16 stimulating contacts.



We have enrolled four people with unilateral below-knee amputations due to trauma in our study. Each participant received three 16-contact composite flat interface nerve electrodes (C-FINEs, Ardiem Medical, Inc., Indiana, PA) around their sciatic, tibial and/or common peroneal nerves (**Figure 6**) (Freeberg, Stone, Triolo, & Tyler, 2017). C-FINEs gently reshape the nerve with minimal exertion of pressure along the length of the nerve. It is constructed from a sandwich of patterned polyether ether ketone (PEEK) within layers of pliable silicone. The PEEK polymer acts as a stiffening bar to enforce an oval cross sectional area, but it is flexible enough to allow bending along the length of the nerve. The opening height of the C-FINE is larger than the largest fascicle, as to not occlude blood flow. All C-FINE contacts in our application were connected to percutaneous leads, which exited the skin on the upper anterior thigh, allowing connection to a custom-designed external stimulator (Bhadra, Kilgore, & Peckham, 2001; B. Smith et al., 1998).

In our previous study, two of these participants were asked to describe the quality, intensity, and location of PNS-evoked percepts (Charkhkar et al., 2018). To avoid biasing or limiting responses, the participants were not given a list of words for describing the quality of a percept. Participants verbally rated perceived intensity on a self-selected scale. If the stimulus was imperceptible, the participants assigned an intensity value equal to zero. If an evoked sensation felt twice as strong as a previous sensation, they would assign an intensity value twice as large as the previously reported value. They were also asked to draw the location of the percept(s) on a blank diagram of a healthy foot and leg.

We found that PNS could evoke somatosensory percepts referred to the missing toes, midfoot, heel, and ankle of both BKAs. The participants reported tactile and proprioceptive sensations, such as pressure, tingling, ankle movement, and toe curling. As charge density increased, the perceived modality of sensory percepts transitioned from tactile to proprioceptive. To further classify the effect of changing pulse width on perceived stimulus intensity, we conducted a psychophysical analysis with four C-FINE contacts. In the forced-choice experiment, the participants received two stimulation-evoked percepts and were asked which one had a higher intensity (Emily L Graczyk et al., 2016). The average just noticeable difference (JND) was 29$\pm$7 µs (mean $\pm$ standard deviation), meaning that the difference in magnitude between two stimuli had to be at least this large in order for participants to detect a difference in intensity. The charge thresholds, meaning the minimum amount of charge needed to evoke a percept, remained stable over the course of seven months.

The most substantial benefit of this technique is that it directly isolated and activated afferent sensory fibers that referred to the missing limb. This made it possible to evoke more natural feelings of foot-floor contact pressure, and the location of feedback can be referred to the expected location on the missing foot rather than the surface of the residual limb. The biggest drawback is that this technique requires invasive surgery. Because extraneural electrodes do not breach the epineurium, they are less invasive than intraneural electrodes. Extraneural electrodes can also be fabricated to conform to the shape of the target nerves in order to minimize applied pressures and maintain blood flow while preserving nerve health (Freeberg et al., 2017).

Functional assessments of sensory-enabled below-knee prostheses

Few studies have actually quantified the impact of sensory feedback during functional tasks performed by unilateral below-knee amputee volunteers. In this section, I review two prior studies and present our results of BKAs performing a sensory organization test with and without using a sensory-enabled prosthesis.

Vibration

When receiving vibratory feedback about the CoP under the foot, below-knee amputees demonstrate no significant balance improvements with respect to standing balance tests, rhythmic weight shift tests, or limits of stability tests (Rusaw et al., 2012). Twenty-four unilateral below-knee amputees received feedback via four vibrating tactors around the circumference of the thigh that relayed information about forces applied to sensors underneath the prosthetic toes, first metatarsal, fifth metatarsal, and heel (**Figure 4**). Vibration strength of each tactor was scaled as a function of the pressure applied to the corresponding sensor. Participants were given ten minutes to acclimate themselves to the device, during which they were asked to lean in different directions. The amputees then performed three tests: standing balance, Limits of Stability (LOS), and Rhythmic Weight Shift (RWS). The standing balance test consisted of four conditions: static standing with the eyes open/closed and standing on a moving platform with the eyes open/closed. During the LOS test, participants were instructed to lean in one of eight directions in the medial-lateral (M/L) and/or anterior-posterior (A/P) plane without moving their feet. During the RWS test, participants leaned in the A/P or M/L plane while following a cursor on a computer screen that dictated their pace. When receiving vibratory feedback, there were no significant improvements in the standing balance or RWS tests. However, during the LOS test, reaction time was faster. The authors suggest that participants may have benefited from a longer familiarization period with the sensory-enabled prosthesis outside of the laboratory. They also suggested that the amputees might not have been able to effectively make use of this vibratory feedback. It is possible that vibratory feedback imposed too much of a cognitive burden: participants had to translate both the location and quality of the vibratory stimuli into pressure information that they recognized. More specifically, they received sensory information on their residual limb regarding prosthetic foot-floor contact, and they had to interpret vibration and relate it to contact pressure, rather than perceiving contact pressure directly.

Electrocutaneous stimulation

When receiving electrocutaneous stimulation feedback regarding contact between the ground and the prosthetic toe or heel, below-knee amputees exhibit a more symmetrical weight distribution during static standing but no improvements with respect to single-leg static standing or level ground walking (J. A. . Sabolich & Ortega, 1994). Three electrodes were placed on the anterior residual calf and three were placed on the posterior residual calf, all underneath the prosthesis socket (**Figure 5**). Force sensors were placed underneath the toes and heel of the prosthesis. Force applied to the toe sensor resulted in stimulation applied to the anterior calf, and heel sensor activation resulted in stimulation of the posterior calf. Stimulation magnitude was not scaled proportionally to the applied forces. Twelve unilateral BKAs participated in a 5-6 hour familiarization period with the device that consisted of walking and taking breaks. To study the functional benefits of electrocutaneous sensory feedback, the amputees performed three tasks: static standing, single-leg static standing, and walking over level-ground at a self-selected speed. While wearing the sensory-enabled prosthesis during static standing, BKAs adopted a more symmetrical weight distribution. There were no significant changes in single-limb standing time or gait characteristics, such as stance-time symmetry and step-length symmetry. The authors hypothesized that a longer familiarization period with the sensory-enabled prosthesis outside of the laboratory could be more beneficial to the users. Scaling the magnitude of electrocutaneous stimulation to the magnitude of force applied to the sensors may also have improved results.

Peripheral nerve stimulation

Intraneural or extraneural electrodes can evoke somatosensory percepts referred to the missing leg of above-knee amputees (Clippinger et al., 1982; Petrini et al., 2019). Functional testing of above-knee prostheses equipped with intraneural sensory feedback occurred over a span of three months for two AKAs (Petrini et al., 2019). Three pressure sensors underneath the prosthetic foot and an encoder in the prosthetic knee triggered stimulation. The sensors triggered stimulation-induced sensations referred to the third metatarsal, fifth metatarsal, heel, or calf of the missing leg. The pulse amplitude of stimulation was linearly scaled to applied force. The above-knee amputees demonstrated an improved walking speed and self-reported confidence, mental fatigue, and physical fatigue.

Above-knee prostheses equipped with intraneural sensory feedback were tested with 13 amputees (Clippinger et al., 1982). The pulse frequency of electrical stimulation was modulated based on readings from strain gauges in the pylon and a piezoelectric crystal in the prosthetic heel. The participants used their systems outside of the laboratory for an average of eight months. The study did not report the effect of sensory feedback on balance or gait measures, but it stated that sensory feedback improved amputees' confidence while walking and functionality in poorly lit areas.

Building on these results, we tested the functional performance of below-knee prostheses equipped with closed-loop extraneural sensory feedback. An unpublished version of this manuscript is included in Appendix A. An array of force-sensitive resistors placed under the prosthetic foot captured the plantar pressure distribution. The pressure data were processed in real time to determine the appropriate C-FINE contact and pulse width for the electrical stimulation. Two below-knee amputees performed a Sensory Organization Test, during which the center-of-pressure under both feet was calculated using force plate measurements. The amputees performed the test with and without the sensory neuroprosthesis active. Postural sway was quantified by calculating the root-mean-square of the A/P and M/L CoP in each test condition. Moreover, the area of the CoP scatter was estimated by fitting an ellipse to the data and calculating its area. Additionally, we compared the changes in body weight distribution between the intact and prosthetic leg. Our results from two below-knee amputees show there was a significant difference in sway when using a sensory neuroprosthesis ($p<0.001$, one-way ANOVA). Tukey post hoc analyses revealed that, in both participants, sensory feedback improved sway when proprioception from the intact leg and the vestibular input were simultaneously perturbed ($p<0.001$). The 2^{nd} participant also showed improved sway with sensory feedback when proprioception in the intact leg was compromised ($p<0.05$). Moreover, when sensory feedback was present, the 2^{nd} participant shifted more body weight onto the prosthesis side if visual or proprioception inputs were perturbed ($p<0.05$). These findings suggest that below-knee amputees can benefit from sensory feedback, especially in challenging conditions when proprioception from the intact leg and vestibular inputs are perturbed.

Summary

In summation, there are over one million lower-limb amputees in the United States alone (Ziegler-Graham et al., 2008). Though there are many different classes of technologically advanced prostheses, below-knee amputees still face functional challenges in everyday situations. During the navigation of level-ground, uneven terrain, stairs, and ramps, below-knee amputees adopt compensatory hip and knee strategies that result in greater muscular effort, higher metabolic cost, slower gait, and gait asymmetry. In the long-term, asymmetrical gait leads to chronic lower back, hip, and knee pain (Norvell et al., 2005). Powered plantarflexion and myoelectric prostheses have had marginal improvements on gait kinematics and kinetics (Kannape & Herr, 2016).

Lower-limb amputees heavily rely on their remaining “postural reserve” of resources to maintain balance, specifically vision, the vestibular system, cognitive attention, and the intact limb. Amputees use a sensory reweighting technique to compensate for missing somatosensory and musculoskeletal feedback from their missing limb, but they still have a higher risk of falling (Kulkarni et al., 1996; William C. Miller, Speechley, et al., 2001) and a lower quality of life than the general population (Sinha et al., 2011). Adding resources such as somatosensation back into the postural reserve could significantly improve both prosthetic functionality and amputees' quality of life.

In healthy feet, plantar somatosensation plays a crucial role in maintaining balance and body posture during locomotion. When plantar sensation is temporarily eliminated in both feet of non-amputees using hypothermic anesthesia, postural sway increases (Billot et al., 2013; Hong et al., 2007), posture is more crouched during gait (Hohne et al., 2012), and more reactive steps are needed to restore equilibrium following perturbations (Perry et al., 2000). If cutaneous information is eliminated in just one foot region, people shift their body weight away from that region during gait (Nurse & Nigg, 2001). The similarities between able-bodied people without sensation and below-knee amputees indicates that some of the functional challenges amputees face are due to a lack of plantar somatosensation.

One approach to improving amputees' quality of life is to improve prosthetic functionality by adding sensory feedback. Auditory cues (Yang et al., 2012), vibration (Marayong et al., 2014; Rokhmanova & Rombokas, 2019; Rusaw et al., 2012; Wan et al., 2016), electrocutaneous stimulation (Dietrich et al., 2018; J. A. Sabolich & Ortega, 1994), and peripheral nerve stimulation (PNS) (Charkhkar et al., 2018; Clippinger et al., 1982) have all been used as methods of sensory feedback. Auditory cues, vibration, and electrocutaneous stimulation are non-invasive techniques with minimal risk. However, they do not resemble typical contact between the foot and an object with respect to stimulus modality and location, which imposes a learning curve.

Electrical PNS can be applied directly to the residual peripheral nerves, such as the sciatic nerve, to evoke somatosensory percepts referred to the plantar surface of the missing foot (Charkhkar et al., 2018; Clippinger et al., 1982; Petrini et al., 2019). Peripheral nerve stimulation is the most invasive technique of those mentioned, but because it can directly isolate and activate neural fibers that innervate the missing foot, it has the most potential for providing natural feedback with a smaller learning curve. Our group has developed an extraneural stimulation method for below-knee sensory neuroprostheses (Charkhkar et al., 2018). We implanted nerve cuff electrodes around the sciatic, common peroneal, and tibial nerves of four unilateral below-knee amputees. Electrical stimulation through these electrodes evokes percepts referred to the missing toes, midfoot, heel, and ankle. The participants report tactile and proprioceptive sensations, such as pressure, tingling, ankle movement, and toe curling.

Few studies have actually quantified the impact of sensory feedback during functional tasks performed by unilateral below-knee amputee volunteers. Feedback from vibration and electrocutaneous stimulation had marginal functional improvements during gait and static and dynamic standing (Rusaw et al., 2012; J. A. . Sabolich & Ortega, 1994). This may be because a longer familiarization period with the device is needed, and/or it may be the mismatch between the expected and actual stimulus quality and location. The functional benefits of intraneural and extraneural stimulation are promising for sensory neuroprostheses (Clippinger et al., 1982; Petrini et al., 2019). In our functional testing, we found that extraneural stimulation could have the biggest impact on BKAs when proprioception from the intact leg and vestibular inputs are perturbed (Appendix A).

CHAPTER 2: Dissertation objectives

Motivation

Over one million individuals in the United States alone have a lower-limb amputation (Ziegler-Graham et al., 2008). Most major lower-limb amputations are due to vascular disease, trauma, and cancer (Ziegler-Graham et al., 2008). Though there are many different classes of technologically advanced prostheses, below-knee amputees still face functional challenges in everyday situations. During the navigation of level-ground, uneven terrain, stairs, and ramps, below-knee amputees adopt compensatory hip and knee strategies that result in greater muscular effort, higher metabolic cost, slower gait, and gait asymmetry (for a complete review, please see Chapter 1). In the long-term, asymmetrical gait leads to chronic lower back, hip, and knee pain (Norvell et al., 2005). Consequently, lower-limb amputees report a lower quality of life than the general population (Sinha et al., 2011).

These challenges can be explained in part by the fact that locomotion is a sensorimotor process, and no commercially available prostheses offer somatosensory feedback. Prior work has shown that the addition of sensory feedback into a prosthesis can improve functional ability (Clark et al., 2014; Dhillon & Horch, 2005; Hebert et al., 2014; Horch et al., 2011; Petrini et al., 2019; Pylatiuk et al., 2006; Stanisa Raspopovic et al., 2014; Rusaw et al., 2012; J. A. Sabolich et al., 2002; Schiefer et al., 2016; Tan et al., 2014), reduce phantom pain (Dietrich et al., 2012; Petrini et al., 2019; Tan et al., 2014), and enhance prosthesis embodiment (the incorporation of a prosthesis into one's body schema) (Arzy et al., 2006; Emily L Graczyk et al., 2018; Marasco et al., 2011; Mulvey et al., 2012; Schiefer et al., 2016). Until recently, sensory feedback was primarily restricted to sensory substitution techniques involving vibration or electrocutaneous stimulation (Bach-y-Rita & W. Kercel, 2003; Cipriani, D'Alonzo, & Carrozza, 2012; S Crea, Cipriani, Donati, Carrozza, & Vitiello, 2015; Dietrich et al., 2012; Geng & Jensen, 2014; Kaczmarek, Tyler, Brisben, & Johnson, 2000; Kaczmarek, Webster, Bach-y-Rita, & Tompkins, 1991; Perovic, 2013; J. A. Sabolich et al., 2002; White, Saunders, Scadden, Bach-Y-Rita, & Collins, 1970). Neither method directly isolates and activates afferent sensory fibers that refer to the missing limb.

We have demonstrated that nerve cuff electrodes implanted around the sciatic, common peroneal, and tibial nerves of below-knee amputees can evoke somatosensory percepts referred to their missing feet (Charkhkar et al., 2018). Though peripheral nerve stimulation (PNS) takes advantage of the existing neural pathways that carry sensory information from the amputated limb to the brain, electrical stimulation does not activate these afferent fibers in the exact same manner as physically-applied natural tactile stimuli. Afferent activation in response to mechanical stimuli involves complex firing patterns of populations of neurons, where the particular fibers activated (SAI, SAII, RAI, or RAII) and temporal firing patterns depend on the tactile stimulus (Roland S Johansson & Flanagan, 2009; Roland S Johansson & Vallbo, 1983). These exact firing patterns cannot be duplicated using existing neural interfaces due to limitations in the number of electrode contacts and the biophysics of electrical neural recruitment (Saal & Bensmaia, 2015).

The differences in neural activation may cause perceptual differences between stimulation-evoked sensation and natural touch with respect to temporal synchrony and multisensory integration. Though there are differences in the physical and neural transmission times of different sensory stimuli, when we see something touch our body, we perceive that the tactile stimulus and visual stimulus occurred at the same time. Previous reports indicate that PNS-evoked sensations are perceived as natural in terms of location and intensity (Charkhkar et al., 2018), but the temporal synchrony of vision and PNS-evoked somatosensation has not been characterized. Additionally, it is critical to quantify if PNS-evoked somatosensation has any noticeable delays. Humans can consciously detect discrepancies greater than 200 ms between different sensory modalities (Franck et al., 2001; Shimada, Hiraki, & Oda, 2005). Visuotactile asynchrony greater than 300 ms significantly compromises the integration of a prosthesis into the body schema of a user (Shimada, Fukuda, & Hiraki, 2009). The characterization of temporal synchrony is crucial for determining if PNS-evoked percepts are perceived as natural sensory inputs and are therefore suitable for sensory neuroprostheses.

In healthy, intact sensory systems, multiple senses interact to maximize perception and establish a redundancy. Previous psychophysical studies have shown that tactile spatial resolution improves by adding vision (Ernst & Banks, 2002; Kennett, Taylor-Clarke, & Haggard, 2001; Taylor-Clarke, Kennett, & Haggard, 2004), and that the nervous system utilizes postural information and cognitive expectations to determine the location of touch (Asai & Kanayama, 2012; E Azañón & Soto-Faraco, 2008; Elena Azañón, Stenner, Cardini, & Haggard, 2015; Heed, Buchholz, Engel, & Röder, 2015; Heed & Röder, 2010; Longo, Mancini, & Haggard, 2015). Multisensory integration helps to ensure that a task is achieved: senses with the least amount of noise/uncertainty and the highest relevance are given the greatest weight (Ernst & Banks, 2002; Fay B. Horak, 2006; Van Der Kooij & Peterka, 2011). As Stein and Stanford stated, the "integrated product of combined sources of information reveals more about the nature of the external event and does so faster and better than would be predicted from the sum of its individual contributors" (B. E. Stein & Stanford, 2008). These multisensory interactions have not been previously demonstrated but they are important for sensory neuroprostheses, which will be used in diverse environments with various sensory resources available. If PNS-evoked somatosensation demonstrates a similar multisensory redundancy, this will improve the fidelity and perhaps the ultimate utility of sensory neuroprostheses in locomotion.

In addition to understanding how PNS-evoked somatosensation is processed and perceived by the nervous system, our next step was to evaluate if the body could utilize this new sensory input to assist with locomotion. The functionality of lower-limb sensory neuroprostheses is not well understood in part because it is challenging to isolate and assess the role of cutaneous plantar sensation. Unilateral lower-limb amputees are missing afferent information from sensory receptors in lost muscles, tendons, and skin of one leg, but can compensate for minor threats to stability by reweighting their remaining resources (A. C. Geurts et al., 1992). In particular, amputees rely on their intact limb and visual inputs during locomotor tasks (Barnett et al., 2013; Isakov et al., 1992). To our knowledge, no existing tests evaluate the role of human plantar sensation in one foot at a time while minimizing compensation by vision. Therefore, there is a need to not only assess the performance of a sensory neuroprosthesis during a challenging locomotor task, but there was also a need to develop a test that could isolate and evaluate the role of cutaneous plantar sensation.

The underlying theme of this dissertation is that temporal synchrony and multisensory integration of stimulation-evoked somatosensory feedback are critical for lower-limb amputees in performing challenging locomotor tasks. A brief overview of the methods and hypotheses for each experimental aim is given in this chapter. Aims 1, 2, and 3 are discussed in detail in Chapters 3, 4, and 5, respectively.

Research Overview

Aim 1

Determine if visuotactile temporal synchrony of stimulation-evoked sensation is different than natural somatosensation.

Methods

To evaluate visuotactile synchrony, two below-knee amputees and two trans-radial amputees performed a simultaneity judgment task. During this task, a visual stimulus was paired with either (1) natural tactile sensation on the intact contralateral limb, or (2) stimulation-induced sensation via nerve cuff electrodes. Natural tactile sensation was administered by a tactor placed on the intact limb, and stimulation-induced sensation was evoked by electrically stimulating through nerve cuff electrodes on residual peripheral nerves. The outcome measures were the point of subjective simultaneity, which represented processing time, and the just noticeable difference, which represented temporal sensitivity. To evaluate the functional implications of synchrony, two participants also performed a functional delay task in which pressure applied to the prosthesis triggered electrical stimulation after a pre-set delay up to 500 ms. Participants answered if stimulation-evoked somatosensory percepts were simultaneous with the applied pressure.

Hypotheses

1. Natural touch and stimulation-induced sensation are indistinguishable with respect to processing time and temporal sensitivity.
2. Processing time, but not temporal sensitivity, is different between trans-radial and below-knee amputees.
3. Processing time, but not temporal sensitivity, is influenced by the perceived intensity of stimulation-induced somatosensation.
4. Temporal synchrony of stimulation-induced somatosensation does not change over time.
5. Amputees can perceive when stimulation is delayed by more than 200 ms.

Aim 2

Assess how visual inputs and postural manipulations affect the size and location of stimulation-evoked somatosensory percepts.

Methods

Two below-knee amputees were instructed to adopt a specific posture while nerve cuff electrodes delivered electrical stimulation to residual peripheral nerves for five seconds. When stimulation ended, participants drew the location of the elicited somatosensory percept on a blank diagram of a foot and leg. In the baseline condition, participants sat down and placed the prosthetic foot on a stool (condition #1). In static standing conditions, the participants stood upright with their eyes closed (#2) or with their eyes open and looking down at the prosthesis (#3). During conditions with added visual inputs, the participants remained seated while watching an experimenter lightly touch the prosthetic plantar forefoot (#4) or rearfoot (#5). During conditions with postural manipulations, the participants stood upright with their eyes closed and adopted a posture that applied a load on either the plantar surface of the prosthetic forefoot (#6) or rearfoot (#7). During conditions with postural manipulations and visual inputs, participants repeated the same postures while looking down at the prosthesis with their eyes open (#8-9). The region of the foot (forefoot, midfoot, rearfoot) in which sensations were reported in the greatest number of the baseline trials was identified as the primary region of interest (ROI). Inputs collocated with the primary ROI were classified as "congruent." Incongruent inputs were applied to the rearfoot when the primary ROI was the forefoot, and vice versa. In every trial, an activation percentage was assigned to each ROI based on how much of the region was covered by evoked percepts. Activation percentages were utilized to compare percepts between experimental conditions.

Hypotheses

1. Changing body position from seated to standing does not impact percept size or location.
2. Congruent visual inputs and postural manipulations focus percepts around the location of the input.
3. Incongruent visual inputs and postural manipulations draw percepts away from the original location and towards the location of the input.

Aim 3

Evaluate how stimulation-evoked plantar sensation affects performance in a challenging locomotor test.

Methods

Volunteers performed a horizontal ladder walking test, adapted for humans, while blindfolded. The spacing between rungs was randomized and changed after every trial. Fourteen able-bodied individuals and six below-knee amputees participated in this study. Two of the below-knee amputees used prostheses equipped with closed-loop PNS-elicited somatosensory feedback in half of the trials. Video recordings were used to assess foot placement accuracy and trial completion time. Plantar pressure distribution was measured for both feet using force-sensing insoles. Foot placement errors were defined as missing a rung, slipping off a rung, stepping on two rungs at once, or stepping on the side rail. The outcome measures were foot placement error rate, trial completion time, and region of the foot used to step on the ladder rung.

Hypotheses

1. Able-bodied individuals will perform this test with fewer foot placement errors and more quickly than amputees. Able-bodied individuals perform this test more quickly and with fewer foot placement errors than amputees.
2. Able-bodied individuals primarily use the forefoot to step on a ladder rung, whereas amputees primarily utilize the forefoot for the intact leg and the rearfoot for the affected leg.
3. During trials in which BKAs use the sensory neuroprosthesis, foot placement accuracy increases and trial time decreases.
4. During trials in which BKAs use the sensory neuroprosthesis, amputees primarily use the forefoot or midfoot to step on ladder rungs.

CHAPTER 3: Visuotactile synchrony of stimulation-induced sensation and natural somatosensation

The following is a copy of the paper "Visuotactile synchrony of stimulation-induced sensation and natural somatosensation" published in the *Journal of Neural Engineering*, Volume 16, on 30 April 2019 (Christie, Graczyk, Charkhkar, Tyler, & Triolo, 2019).
DOI: https://doi.org/10.1088/1741-2552/ab154c

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Abstract

Objective: Previous studies suggest that somatosensory feedback has the potential to improve the functional performance of prostheses, reduce phantom pain, and enhance embodiment of sensory-enabled prosthetic devices. To maximize such benefits for amputees, the temporal properties of the sensory feedback must resemble those of natural somatosensation in an intact limb. *Approach*: To better understand temporal perception of artificial sensation, we characterized the perception of visuotactile synchrony for tactile perception restored via peripheral nerve stimulation. We electrically activated nerves in the residual limbs of two trans-tibial amputees and two trans-radial amputees via non-penetrating nerve cuff electrodes, which elicited sensations referred to the missing limbs. *Main results*: Our findings suggest that with respect to vision, stimulation-induced sensation has a point of subjective simultaneity (processing time) and just noticeable difference (temporal sensitivity) that are similar to natural touch. The just noticeable difference was not significantly different between the participants with upper- and lower-limb amputations. However, the point of subjective simultaneity indicated that sensations evoked in the missing leg must occur significantly earlier than those in the hand to be perceived as maximally synchronous with vision. Furthermore, we examined visuotactile synchrony in the context of a functional task during which stimulation was triggered by pressure applied to the prosthesis. Stimulation-induced sensation could be delayed up to 111 ± 62 ms without the delay being reliably detected. *Significance*: The quantitative temporal properties of stimulation-induced perception were previously unknown and will contribute to design specifications for future sensory neuroprostheses.

Introduction

Over two million people are living with limb loss in the United States (Ziegler-Graham et al., 2008). Although there are many different commercially available prostheses, only 59% of upper-limb amputees and 88% of lower-limb amputees report using them routinely in activities of daily living (Giummarra et al., 2010). One contributing factor is that feedback provided by a prosthesis is limited: users primarily rely on visual and auditory cues, as well as pressure exerted by the prosthesis onto the residual limb (Childress, 1980; S Crea et al., 2015; Fernie & Holliday, 1978). While such feedback mechanisms help users to operate their prostheses, current devices are often not sufficient for navigating in challenging environments or performing intricate movements.

Prior work has shown that the addition of sensory feedback into a prosthesis can improve functional ability (Clark et al., 2014; Dhillon & Horch, 2005; Hebert et al., 2014; Horch et al., 2011; Pylatiuk et al., 2006; Stanisa Raspopovic et al., 2014; Rusaw et al., 2012; J. A. Sabolich et al., 2002; Schiefer et al., 2016; Tan et al., 2014), reduce phantom pain (Dietrich et al., 2012; Tan et al., 2014), and enhance prosthesis embodiment (the incorporation of a prosthesis into one's body schema) (Arzy et al., 2006; Emily L Graczyk et al., 2018; Marasco et al., 2011; Mulvey et al., 2012; Schiefer et al., 2016). Until recently, sensory feedback was primarily restricted to "sensory substitution" techniques involving vibration or electrical stimulation applied to the skin of the residuum (Bach-y-Rita & W. Kercel, 2003; Cipriani et al., 2012; S Crea et al., 2015; Dietrich et al., 2012; Geng & Jensen, 2014; Kaczmarek et al., 2000, 1991; Perovic, 2013; J. A. Sabolich et al., 2002; White et al., 1970). Neither method directly isolates and activates afferent sensory fibers that refer to the missing limb.

Peripheral nerve stimulation (PNS) takes advantage of the existing neural pathways that carry sensory information from the amputated limb to the brain. Though PNS activates the same afferent fibers as mechanical tactile stimuli, it does not activate these fibers in the same way. Afferent activation in response to mechanical stimuli involves complex firing patterns of populations of neurons, where the particular fibers activated and patterns of firing depend on the spatial and temporal properties of the tactile stimulus (Roland S Johansson & Flanagan, 2009; Roland S Johansson & Vallbo, 1983). Current neural stimulation paradigms do not achieve the same neural activation patterns as mechanical stimuli. Despite these differences, direct activation of the peripheral sensory nerves in an amputee's residual limb via chronically implanted neural interfaces successfully evoked somatosensory perceptions referred to and co-located with the missing limb (Charkhkar et al., 2018; Clark et al., 2014; Dhillon, Krüger, Sandhu, & Horch, 2005; Hebert et al., 2014; S Raspopovic et al., 2014; Tan et al., 2014). To maximize the benefits of sensory feedback incorporated into a prosthesis and to more closely mimic an intact limb, sensations from PNS must emulate the temporal characteristics of the intact limb's tactile sensation. If cognitive perception of a tactile stimulus is delayed by even 200 ms, it can significantly compromise the integration of a prosthesis into the body schema of a user (Shimada et al., 2009). Because of the differences in fiber activation between stimulation-induced sensation and natural tactile sensation, it is possible that their temporal integration with multisensory inputs to promote embodiment could be different, too. Yet, temporal properties of sensations elicited by PNS have not been well characterized.

We previously demonstrated somatosensory restoration using implanted non-penetrating nerve cuff electrodes around the residual peripheral nerves of trans-radial (Tan et al., 2014) and trans-tibial amputees (Charkhkar et al., 2018). Because the elicited sensations were perceived to be natural in terms of location and intensity, we hypothesized that they may also mimic the temporal properties of natural sensation. In this work, we used a visuotactile simultaneity judgment task to compare the temporal processing of PNS-induced sensation ("artificial" touch) to intact tactile perception ("natural" touch). We hypothesized that natural touch and sensation elicited by PNS would be indistinguishable with respect to the point of subjective simultaneity and just noticeable difference. To determine the functional implications of visuotactile synchrony, participants also performed a "functional delay task" in which pressure applied to the prosthesis triggered stimulation-induced sensation after a set delay. Validation of the functional implications of perceived synchrony is unique in the psychometric literature, because it is normally not possible to delay tactile stimuli in this manner in the intact somatosensory system.

Methods

Research participants

Two people with unilateral trans-tibial amputations (LL01 & LL02) and two people with unilateral trans-radial amputations (UL01 & UL02) due to trauma were enrolled in this study. At the time of device implantation, LL01 was 67 years old, LL02 was 54 years old, and both UL01 and UL02 were 46 years old. All four participants were male, regular prosthesis users, and did not have peripheral neuropathy or uncontrolled diabetes. The Louis Stokes Cleveland Veterans Affairs Medical Center Institutional Review Board and Department of the Navy Human Research Protection Program approved all procedures. This study was conducted under an Investigational Device Exemption obtained from the United States Food and Drug Administration. All participants gave their written informed consent to participate in this study that was designed in accordance with relevant guidelines and regulations.

Implanted technology

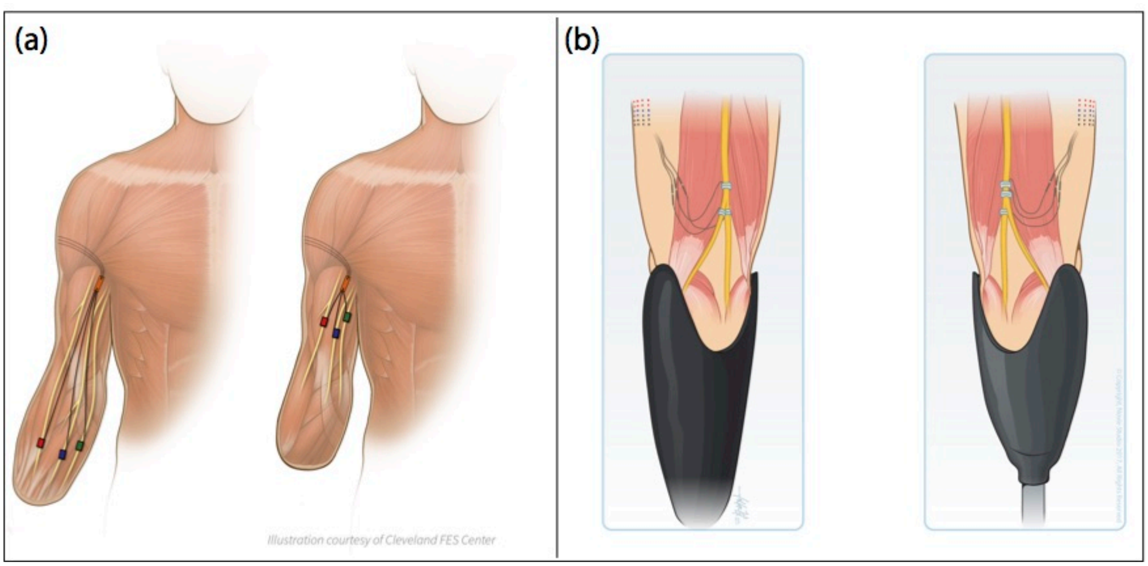
The two participants with upper-limb amputations (ULA) received surgically-implanted 8-contact Flat Interface Nerve Electrodes (FINEs) that wrapped around the nerves (Tyler & Durand, 2002). FINEs were installed on the median and ulnar nerves of participant UL01 in 2012, and median and radial nerves of participant UL02 in 2013 (**Figure 7**a) (Tan et al., 2014). All electrode contacts were connected to open-helix percutaneous leads via spring-and-pin connectors (Ardiem Medical, Inc.). The percutaneous leads exited the skin on the upper anterior arm.

The two participants with lower-limb amputations (LLA) had 16-contact composite Flat Interface Nerve Electrodes (C-FINEs) (Freeberg et al., 2017) installed around their sciatic, tibial and/or common peroneal nerves (**Figure 7**b) (Charkhkar et al., 2018). C-FINEs are an updated version of the FINE; they have the same electrode size and mechanism of nerve excitation, but they are more compliant and have less volume while maintaining equivalent performance (Freeberg et al., 2017).

The additional compliance of the C-FINEs makes them more suitable for implant locations close to joints, such as in the popliteal fossa near the knee for trans-tibial amputees. Both participants were implanted in 2016. All C-FINE contacts connected to percutaneous leads via industry-standard 8-contact in-line connectors (Medtronic Inc.). The percutaneous leads exited the skin on the upper anterior thigh.

Figure 7: *Location of nerve cuff electrodes for participants with trans-radial or trans-tibial amputations.*

(a) Three nerve cuff electrodes were implanted around the radial, median, and ulnar nerves of participants UL01 (left) and UL02 (right). The small red square represents the electrode on the radial nerve, the blue represents the median nerve, and the green represents the ulnar nerve. Drawing is courtesy of the Cleveland FES Center. (b) Three 16-contact C-FINEs were implanted around the sciatic, tibial, and common peroneal nerves of participant LL01 (left) and around the proximal sciatic, distal sciatic, and tibial nerves of participant LL02 (right). Reproduced from (Charkhkar et al., 2018). © IOP Publishing Ltd. CC BY 3.0. And printed with permission from © Novie Studio.



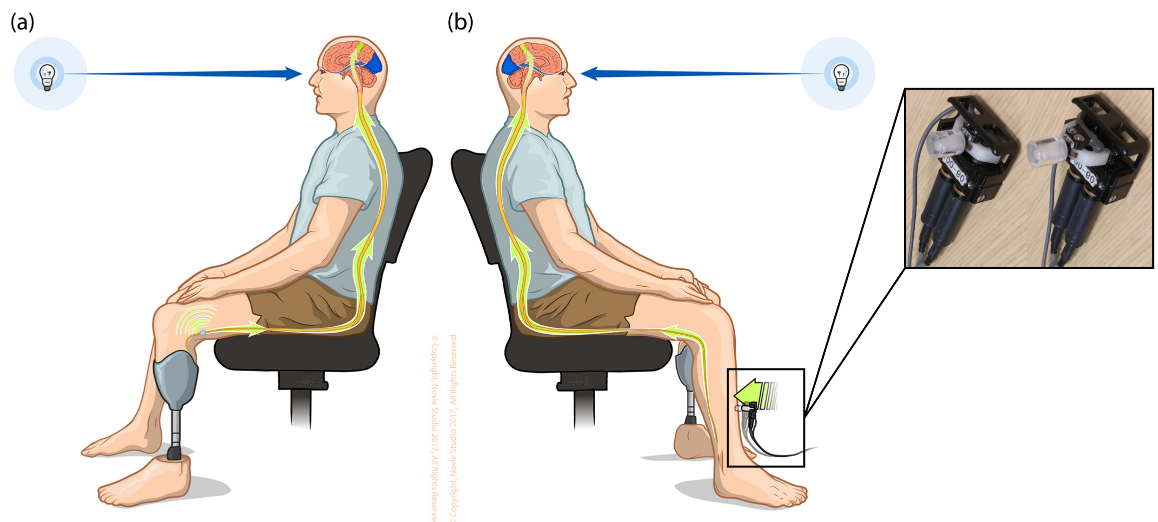
For all participants, percutaneous leads connected to a custom-designed external stimulator (Bhadra et al., 2001; B. Smith et al., 1998) that had 24 current-controlled output channels, a maximum stimulation amplitude of 5.6 mA, a maximum stimulation pulse width of 255 μs, and a compliance voltage of 50 V. Stimulation waveforms were monopolar, asymmetric biphasic, charge-balanced, cathodic-first pulses with return to a common anode placed on the skin of the hip or elbow for the LLA and ULA participants, respectively. Stimulation parameters were set in MATLAB (MathWorks Inc.) and then sent to a single board computer running xPC Target (MathWorks Inc.), which controlled the stimulator in real time. An isolator between the xPC target computer and the stimulator ensured optical isolation between the participant and line-powered instruments. Stimulation was limited to a charge density of 0.5 $\mu C/mm^2$ in order to minimize the risk of tissue and/or electrode damage (Shannon, 1992).

Visuotactile simultaneity judgment task

To evaluate visuotactile synchrony, participants performed a simultaneity judgment (SJ) task (Keetels & Vroomen, 2012). During this task, a visual stimulus was paired with either 1) natural tactile sensation on the intact contralateral limb, or 2) stimulation-induced sensation via nerve cuff electrodes. The visual stimulus was a 10 mm blue light-emitting diode (LED, luminance=7000 mcd) positioned in front of the observer at a distance of ~3 ft. Natural tactile stimuli were administered by a G10 tactor (Kim, Colgate, Santos-MunnÉ, Makhlin, & Peshkin, 2010) (Kinea Design LLC, Evanston, IL, USA) placed on top of the contralateral intact ankle for the LLA participants (**Figure 8**b), and on the anterior surface of the palm of the intact hand for the ULA participants.

Figure 8: *Simultaneity judgment task experimental set-up.*

Two versions of the task were administered: **(a)** Temporal comparison of a visual stimulus to stimulation-induced sensation. **(b)** Temporal comparison of a visual stimulus to a natural tactile sensation administered by a tactor placed on the contralateral intact limb. This illustration depicts the set-up for the trans-tibial amputees; for the trans-radial amputees, the tactor was placed on their contralateral intact hand. The inset shows the tactor in the starting position (left) and the protruded position (right). Printed with permission from © *Novie Studio*.



The tactor was secured to the body with Velcro straps but was not pre-indented on the skin. The tactor was programmed to move in a set direction to exert a pre-defined force of approximately 6 N. This force level was selected to be easily detectable and comfortable for each participant. At the start of the trial, the tactor protruded to apply pressure (not vibration) to the skin (inset of **Figure 8**). Stimulation-induced sensation was produced by delivering 2-sec pulse trains to individual contacts of the cuff electrodes at suprathreshold stimulation levels. Sensory detection thresholds were first found through a forced-choice two-alternative tracking paradigm (Kaernbach, 1990).

Two versions of the SJ task were administered: 1) temporal comparison of natural tactile sensation in the contralateral intact limb vs. a visual stimulus (**Figure 8**b), 2) temporal comparison of stimulation-induced sensation referred to the amputated limb vs. a visual stimulus (**Figure 8**a). The visual and tactile stimuli were sequentially presented, separated by a stimulus onset asynchrony (SOA) value between -500 ms (tactile stimuli first) to +500 ms in 50 ms steps. Order of application of the 21 SOA values was randomized and each SOA was tested ten times per electrode contact. The participants used a touch screen graphical interface to select one of three response categories: the stimuli were "synchronous," "asynchronous – Stimulus X first," or "asynchronous – Stimulus Y first." For the "tactor vs. vision" condition, Stimulus X was the sensation from the tactor and Stimulus Y was the LED. For the "stimulation vs. vision" condition, Stimulus X was the stimulation-elicited sensation and Stimulus Y was the LED. Each trial began with an auditory cue followed by a fixed 2-sec delay to allow the participant to concentrate on the task. This fixed 2-sec delay and the randomized SOA values minimized the effects of learning or anticipation of timing. The electrical stimulation, tactor, and LED were all activated and controlled via xPC Target, which enabled syncing capabilities, real-time control, and data conversion at one millisecond precision. The raw tactor data were adjusted by 22 ms (N=3), which was the measured delay between trial initiation and when the pre-defined maximum force was reached. This delay was measured by using displacement signals produced by an output channel of the tactor.

In the "stimulation vs. vision" condition, stimulus levels were selected such that they were far enough above the charge threshold to be easily and reliably detected by the participant, but not uncomfortable. Participants verbally rated perceived intensity on a self-selected scale. If the stimulus was imperceptible, the participants assigned an intensity value equal to zero. If an evoked sensation felt twice as strong as a previous sensation, they would assign an intensity value twice as large as the previously reported value. The parameters for each experiment were selected such that the sensation intensity was approximately matched across contacts within each participant. The electrical stimulation in each trial was turned on with a single set of parameter values, and the stimulation parameters did not vary during the stimulus "on" period. Thus, the electrical stimulation was a step function, not a ramp. Table 3 contains the location and quality of evoked sensations.

Table 3: The participants' most recent descriptions of the location and quality of the stimulation-induced sensation.

In the second column, 'S', 'DS,' 'T', 'P', 'M', and 'R' stand for sciatic, distal sciatic, tibial, common peroneal, median, and radial nerve cuff electrodes. The numbers indicate the contact number within the cuff.

	Electrode contact	**Location of evoked sensation**	**Quality of evoked sensation**
UL01	M2	Tip of index and middle fingers	Tingling
	M3	Thumb; webbing of the thumb	Poking; tingling
	M4	Thenar eminence	Vibration; light pressure
UL02	M4	Index finger	Fast tapping
	M6	Dorsal surface of thumb	Tapping
	M7	Thenar eminence	Vibration
	M8	Index finger	Vibration, contraction
	R8	Dorsal surface of thumb	Vibration, contraction
LL01	S2	Big toe	"Like I'm trying to push the big toe down"
	S13	Big toe	"Like someone put a finger on it and was pushing down"
	S14	Big toe	"Pushing down"
	P2	Medial side of residual calf	Poking
LL02	DS1	Top surface of the foot	Pressure
	DS3	Posterior lateral side of the foot	Tingling
	T1	Lateral ankle; residual calf	Tingling; tightening
	T13	Medial side of the foot	Tingling

For the LLA participants, a total of eight C-FINE contacts were tested for the "stimulation vs. vision" condition. Pulse frequency varied between C-FINE contacts from 20-100 Hz, pulse width varied between 130-250 μs, and pulse amplitude varied between 0.7-2.4 mA. Prior work suggests that stimulus intensity could impact temporal synchrony (Jaśkowski, 1999; Neumann & Niepel, 2004; Sanford, 1971; David I Shore & Spence, 2005; W. F. Smith, 1933). To examine this effect, we selected two C-FINE contacts per LLA participant for which PSS and JND values were furthest from the "tactor vs. vision" results. Subsequently, we re-tested these four contacts with stronger stimulation parameters. We raised the magnitude of an evoked sensation by increasing pulse width, pulse amplitude, and/or pulse frequency (Emily L Graczyk et al., 2016). New stimulus parameters were selected based on verbal ratings that participants gave to the perceived intensity of the evoked sensation. To identify new stimulus parameters, the reported intensity of sensation had to increase by at least 25%.

For the ULA participants, a total of eight FINE contacts were tested for the "stimulation vs. vision" condition. During the first set of experiments in 2014, stimulation pulse frequency was 125 Hz and pulse amplitude and pulse width were selected to be suprathreshold and comfortable, as described above. In addition, the pulse width of each stimulus varied sinusoidally over a 5-10 μs range about this selected pulse width with a 1 Hz envelope. The sinusoidal pulse width modulation was intended to improve the quality of the sensations, following earlier work on this approach described in Tan *et al.* 2014 (Tan et al., 2014). The stimulus pulse width range was selected per contact to ensure that stimuli were perceptible, comfortable, and had optimal perceived quality throughout the duration of the stimulus. To study the effects of long-term exposure to sensory stimulation on perceived synchrony, the experiments were repeated 3.5-4 years later in 2017-2018. The testing protocol was the same across both sets of experiments. We selected stimulation parameters that best approximated the reported intensities of the previously evoked sensations. Pulse frequency varied between 20-100 Hz, pulse width varied between 120-250 μs, and pulse amplitude varied between 0.5-1.3 mA.

For each electrode contact, 210 trials were required to generate one PSS value and one JND value. We collected trial sets to generate four PSS and JND values for LL01 with low intensity stimulation, two values for LL01 with high intensity stimulation, four values for LL02 with low intensity stimulation, two values for LL02 with high intensity stimulation, two values with UL01 in 2014 (three contacts were tested, though the results from one contact were discarded due to poor curve fitting results, as described in the 'Outcome measures' section), three values with UL01 in 2017-2018, five values with UL02 in 2014, and five values with UL02 in 2017-2018. One PSS and JND value were collected for each participant for the "tactor vs. vision" condition. Experiments occurred between post-implant months 9-15 and 4-10 for participants LL01 and LL02, respectively. For participant UL01, the 2014 experiments occurred in post-implant month 23 and the 2017-2018 experiments occurred between post-implant months 64-70. For participant UL02, the 2014 experiments occurred in post-implant month 15 and the 2017-2018 experiments occurred between post-implant months 57-60. Each experimental session lasted approximately three hours, including time for breaks. Trials were randomized between different electrode contacts in each session in order to minimize any effects of learning or adaptation (Emily Lauren Graczyk, Delhaye, Schiefer, Bensmaia, &

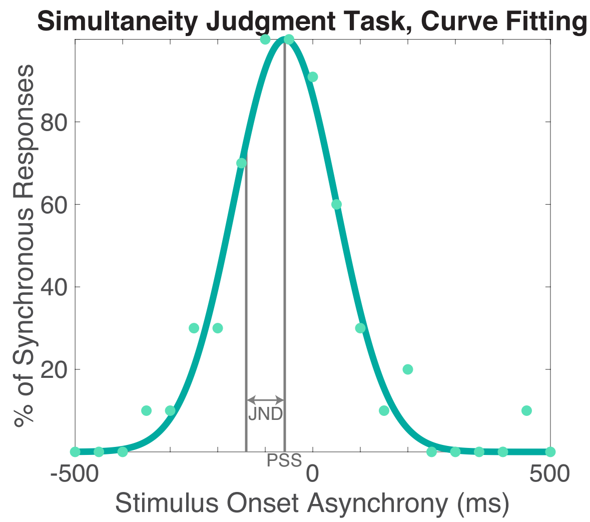
Tyler, 2018). On average, it took 2-3 sessions to collect an entire dataset for each contact per participant.

Identification of noticeable tactile delays in a "functional delay task"

To determine the functional translation of simultaneity judgment task results, participants LL02 and UL01 performed a task using closed-loop stimulation incorporated into the prosthesis. Pressure applied to a force-sensitive resistor (FSR; *IEE, Luxembourg*) triggered stimulation. The sensor had an actuation force as low as 3.6 psi, and readings were acquired every millisecond via a Data Acquisition Board (PCI 6071E, NI, TX). The FSR was affixed externally to avoid any confounding factors due to the placement of the sensor inside a prosthesis. For LL02, the FSR was underneath the third metatarsal region of the prosthetic foot. The participant stood with his prosthesis elevated and then placed it onto the ground after an auditory cue signaled the start of the trial. Participant UL01 applied pressure to an FSR with his prosthetic hand. Neural stimulation, delayed by a pre-determined SOA, was triggered by pressure applied to the FSR. Stimulation parameters did not vary as a function of pressure: they were simply on or off. The SOAs varied from 0-500 ms in 50 ms steps, and were applied in random order. Participants reported whether the perceived stimulation-induced sensation was synchronous with the physical contact applied to the prosthesis or asynchronous. Two electrode contacts were tested per participant; all four contacts were tested in the SJ tasks.

Figure 9: *Curve fitting example and simultaneity judgment task outcome measures.*

Each light green dot is a raw data point that defines a percentage of synchronous responses across ten trials for a given stimulus onset asynchrony (SOA). A Gaussian curve fit to the raw data was used to define two outcome measures: the point of subjective simultaneity (PSS) and the just noticeable difference (JND). Positive SOA values indicate that the visual stimulus came first.



Outcome measures

Following the method detailed in Stone *et al.* (Stone et al., 2001), the psychometric curve describing simultaneity judgment was defined by a Gaussian curve. The percentage of "synchronous" responses was plotted as a function of SOA, and fit to a Gaussian curve limited to 100% (**Figure 9**). Because temporal synchrony results are affected by stimulus intensity (Jaśkowski, 1999; Neumann & Niepel, 2004; Sanford, 1971; David I Shore & Spence, 2005; W. F. Smith, 1933), the raw data from multiple contacts were not combined and fit to one curve. Though stimulus parameters for each electrode contact were selected such that the participant assigned similar ratings to the perceived intensity of the evoked sensation, we did not assume that they were identical. Gaussian curve fitting was acceptable only if the goodness of fit (R^2) was above 0.5.

Only one contact fell below this R^2 threshold and was discarded: contact UL01 M2 in the early 2014 experiments.

Since the functional delay tasks were volitional, it was not possible to predict the initiation of pressure on the FSR, and therefore not possible to have a negative delay (defined as stimulation preceding the pressure on the FSR). While SOA values for the SJ task were negative and positive, they were only positive for the functional delay task (pressure on the FSR precedes stimulation).

Two measures were extracted from the psychometric curve: the point of subjective simultaneity (PSS) and the just noticeable difference (JND) (**Figure 9**). The PSS is the SOA value at which the two stimuli are perceived as maximally simultaneous (Stone et al., 2001), and represents the processing time of tactile stimuli relative to visual stimuli. Processing time consists of both the physical and neural transmission time in addition to the time it takes for stimuli to be consciously perceived. The JND is the time difference between the PSS and the SOA that corresponds to 75% simultaneity. The JND is the smallest temporal interval that observers can reliably discriminate and represents temporal sensitivity (Keetels & Vroomen, 2012).

Statistical analyses

We performed a 2-way ANOVA analysis with fixed factors of amputation level (upper-limb, lower-limb) and stimulus condition (stimulation vs. vision, tactor vs. vision). Separate analyses were performed for dependent variables PSS and JND. In all analyses, significance levels of $\alpha = 0.05$ defined a statistically significant result. There were no outliers in the data and the assumption of normality was not violated (as assessed by Shapiro-Wilk's test of normality).

We also performed one-sample t-tests to compare the high intensity values (N=4 contacts, two from LL01 and two from LL02) to the tactor (the average from LL01 and LL02), and the 2014 “stimulation vs. vision” results (N=7 contacts, two from UL01 and five from UL02) to the tactor (the average from UL01 and UL02). Paired t-tests were used to compare low intensity versus high intensity “stimulation vs. vision” results (N=4 contacts, two from LL01 and two from LL02) and 2014 versus 2017-2018 “stimulation vs. vision” results (N=7 contacts, two from UL01 and five from UL02). A paired t-test also compared the delay values that corresponded to 75% synchronous responses from “stimulation vs. vision” experiments (N=4 contacts, two from UL01 and two from LL02) and functional delay experiments.

Results

Perception of visuotactile synchrony

For participants with upper-limb amputations, the PSS was -24±23 ms for natural tactile sensation and 0±26 ms for stimulation-induced sensation, with respect to vision (**Figure 10**, Table 4). In **Figure 10**a, there is a shaded grey region from -20 ms to +20 ms that depicts the PSS range found in previous studies when comparing vision to finger tapping in able-bodied individuals (Fujisaki & Nishida, 2009; Takahashi, Saiki, & Watanabe, 2008). The JND was 79±11 ms for natural tactile sensation and 91±19 ms for stimulation-induced sensation.

Table 4: Simultaneity judgment task results.

Negative PSS values indicate that the tactile stimulus preceded the visual stimulus. Mean±standard deviation is listed with the number of electrode contacts in parentheses.

	Tactor vs. Vision	**Stimulation vs. Vision**	**Stimulation vs. Vision, High Intensity**	**Stimulation vs. Vision, 2014**
PSS (ms)				
Upper-limb amputees	24±23 (N=2)	0±26 (N=8)		-21±42 (N=7)
Lower-limb amputees	-59±3 (N=2)	-85±44 (N=8)	-38±30 (N=4)	
JND (ms)				
Upper-limb amputees	79±11 (N=2)	91±19 (N=8)		247±79 (N=7)
Lower-limb amputees	83±16 (N=2)	105±24 (N=8)	73±32 (N=4)	

For lower-limb amputees, the PSS was -59±3 ms for natural tactile sensation and -85±44 ms for stimulation-induced sensation, with respect to vision (**Figure 10**, Table 4). The JND was 83±16 ms for natural tactile sensation and 105±24 ms for stimulation-induced sensation.

Effect of stimulus intensity on visuotactile synchrony

For lower-limb amputees, when stimulation parameters were increased, the PSS became significantly closer to zero (p=0.04) and the JND decreased (p=0.04). The high intensity PSS was -38±30 ms and the JND was 73±32 ms (**Figure 11**). Neither the low intensity stimulation nor the high intensity stimulation results were significantly different from the natural touch delivered by the tactor. Participants reported that the evoked sensations felt noticeably stronger no matter which stimulation parameter was changed (pulse width, amplitude, and/or frequency).

__Figure 10:__ Visuotactile synchrony results.

The "tactor vs. vision" results are shown in orange and the "stimulation vs. vision" results are shown in teal. **(a)** The results from electrode contacts tested with participant UL01 have solid lines and the results from UL02 have dashed lines. The shaded grey region demonstrates the PSS range found in able-bodied individuals when comparing vision to finger tapping (Fujisaki & Nishida, 2009; Takahashi et al., 2008). **(b)** The results from participant LL01 have solid lines and the results from LL02 have dashed lines. **(c)** The mean and standard deviation of the PSS values for each amputation level: ULA (upper-limb amputees) and LLA (lower-limb amputees). The black bracket with an asterisk signifies that there was a significantly different PSS between upper- and lower-limb amputees in the "stimulation vs. vision" condition (ANOVA, p=0.001). **(d)** The mean and standard deviation of the JND values for each amputation level. There were no significant differences.

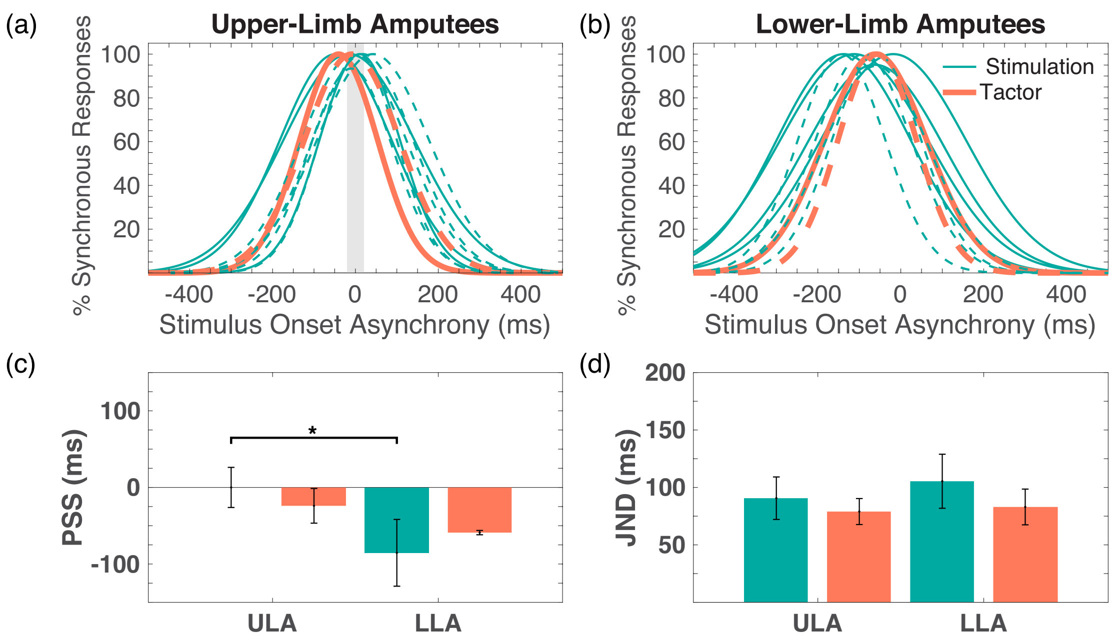
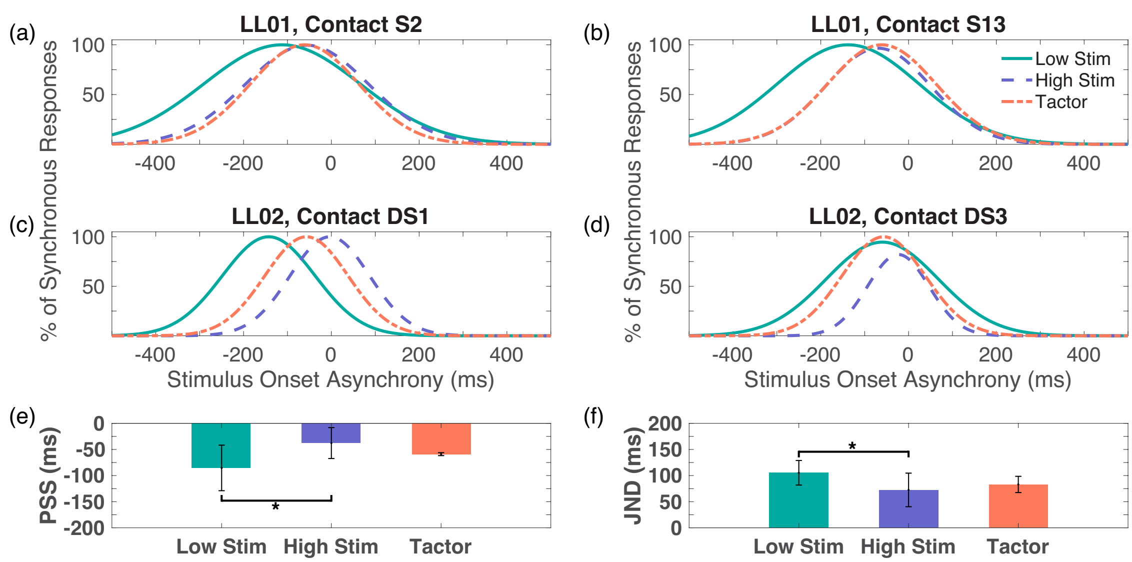


__Figure 11:__ Effect of stimulus intensity on temporal synchrony.

We repeated the "stimulation vs. vision" experiment with two contacts per LLA participant, increasing the stimulation levels in order to evoke sensations that were perceived as having a higher intensity. **(a-d)** The dashed orange curves represent the results of the "tactor vs. vision" experimental condition; solid teal lines are the "stimulation vs. vision" results at a lower intensity, and the dashed purple lines depict the high intensity results. In the subtitles, 'DS' stands for 'distal sciatic' nerve cuff electrodes and 'S' stands for sciatic. The numbers indicate the contact number within the cuff. **(e)** The mean and standard deviation of PSS for the low- and high-intensity "stimulation vs. vision" conditions. The black bracket with an asterisk signifies that PSS was significantly different between high-intensity and low-intensity stimulation (paired t-test, p=0.04). **(f)** The mean and standard deviation of JND for the low- and high-intensity "stimulation vs. vision" conditions. The JND was significantly different between high-intensity and low-intensity stimulation (paired t-test, p=0.04).

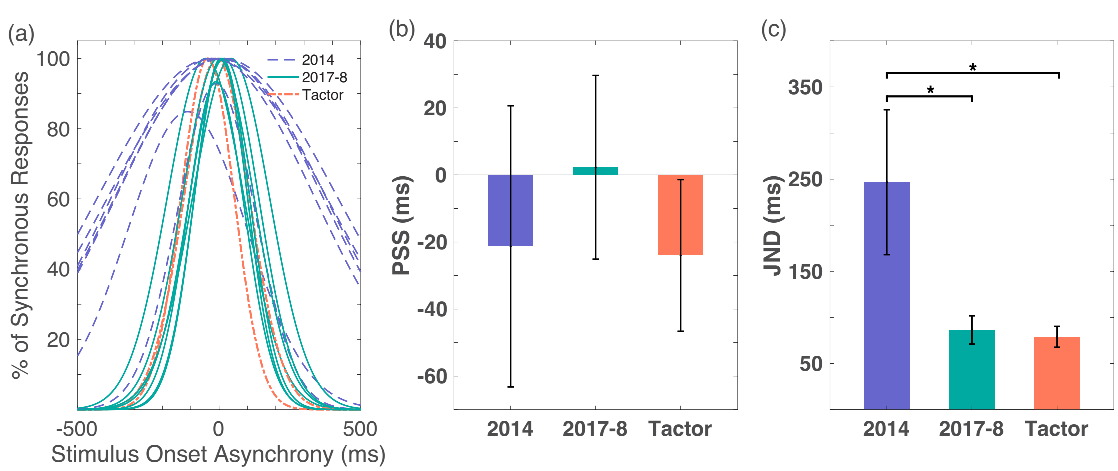


Changes in visuotactile synchrony over time

For upper-limb amputees, the PSS values collected in the "stimulation vs. vision" experiments in 2014 were not significantly different than the PSS values collected in 2017-2018 (**Figure 12**, Table 4), implying long-term consistency of perceived simultaneity. There was a significant decrease in JND over time ($p<0.0001$): the previous JND was 247$\pm$79 ms in 2014, whereas the JND in 2017-2018 was 91$\pm$19 ms.

Figure 12: *Changes in temporal synchrony over time.*

For both ULA participants, we performed two sets of experiments that occurred 3.5-4 years apart. **(a)** The results from the 2014 "stimulation vs. vision" experiments are represented with dashed purple lines (each electrode contact has a separate line), the 2017-2018 "stimulation vs. vision" results are shown with solid teal lines, and "tactor vs. vision" results are in dashed orange lines. Because 2014 data for participant UL01 contact M2 was discarded, the 2017-2018 data for contact M2 was not included in the paired t-tests or in this figure. **(b)** The mean and standard deviation of PSS for the 2014 and 2017-2018 "stimulation vs. vision" conditions. There were no statistically significant differences. **(c)** The mean and standard deviation of JND for the 2014 and 2017-2018 "stimulation vs. vision" conditions. The JND was significantly different between 2014 and 2017-2018 (paired t-test, $p<0.0001$) and between 2014 "stimulation vs. vision" and "tactor vs. vision" (one sample t-test, $p=0.001$).



Comparing natural tactile sensation versus stimulation-induced sensation

The PSS and JND values of natural tactile sensation and stimulation-induced sensation were not significantly different (**Figure 10**). The two-way ANOVA analysis did not determine a statistically significant two-way interaction between stimulation condition and amputation level for PSS or JND. There were also no significant main effects for stimulus condition.

Comparing visuotactile synchrony in ULA versus LLA participants

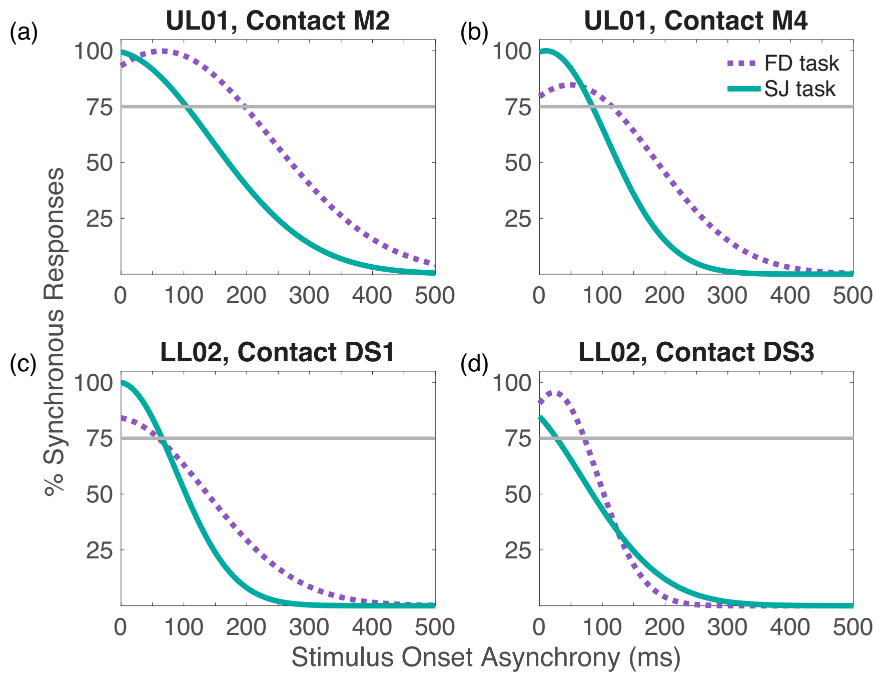
The PSS was significantly different between upper-limb amputees and lower-limb amputees, but the JND was not (**Figure 10**). There was a statistically significant main effect for amputation level with respect to PSS ($p=0.001$) but not to JND. The PSS difference between ULA participants ($N=8$ contacts from 2017-2018 data collection) and LLA participants was 85 ms for the low intensity “stimulation vs. vision” ($N=8$) and 38 ms for high intensity “stimulation vs. vision” ($N=4$).

Acceptable stimulation delays

For the functional delay task, we defined simultaneity to be the delay at which the sensation was perceived as synchronous with the prosthesis touching an object at least 75% of the time. Stimulation had to occur within 66 ± 8 ms for participant LL02 and within 156 ± 57 ms for participant UL01 in order to be perceived as simultaneous with the prosthesis touch (**Figure 13**). On average (across all electrode contacts in both participants), the acceptable delay range was 111 ± 62 ms. For all four contacts, the SOA

Figure 13: *Validation of the functional implications of perceived synchrony.*

The results of the functional delay (FD) task (dashed, purple) in comparison to the "stimulation vs. vision" results of the simultaneity judgment (SJ) task (solid, teal). In each subplot, a horizontal gray line marks the delay at which stimuli were perceived as synchronous at least 75% of the time.



values that corresponded to 75% simultaneity were not significantly different between the functional delay task and the simultaneity judgment task.

Discussion

We performed a visuotactile simultaneity judgment task with four amputees using tactile stimuli that originated either from a mechanical press on the intact limb or from extraneural stimulation applied to the somatosensory nerves in the residual limb. Two of these participants also performed a functional delay task that decoupled visual and tactile stimuli: pressure applied to the prosthesis triggered stimulation-induced sensation after a set delay. In the SJ task, participants were able to perceive the electrical stimulation as touch input and compare the timing between tactile stimuli and visual stimuli. We found that the PSS (which represents processing time) and the JND (which represents temporal sensitivity) for electrically-elicited sensation were not significantly different than natural tactile sensation. The similarity in visuotactile temporal synchrony provides further evidence that extraneural stimulation-induced sensation is processed in broadly the same way as natural touch (Emily L Graczyk et al., 2016; Emily Lauren Graczyk et al., 2018). The SJ experiment and functional delay task did not yield different results, mitigating the need to verify temporal synchrony using a closed-loop sensory neuroprosthesis.

Our findings indicate that the type of tactile stimulus (extraneural stimulation-induced sensation versus physical touch) does not affect JND. Such an observation is consistent with prior work evaluating different types of tactile stimuli with able-bodied individuals (Fujisaki & Nishida, 2009; Harrar & Harris, 2005; Machulla, Di, & Ernst, 2016). Previous visuotactile SJ task studies with able-bodied individuals found JND values of ~55 ms (Fujisaki & Nishida, 2009) and ~94 ms (Harrar & Harris, 2005) with touch applied to the hand. Similarly, we measured a JND of 80$\pm$11 ms when tapping the intact palm of the two ULA participants. We also measured a comparable JND of 91$\pm$19 ms when stimulation-induced sensation evoked a sensation in the phantom hand of the two ULA participants. Similar observations were also noted in a forced-choice "temporal order judgment (TOJ) task" where able-bodied participants had to answer which came first: the flash of an LED or a tactile stimulus applied to the foot (Harrar & Harris, 2005). The measured JND was ~70 ms. In our study, LLA participants had a JND of 83$\pm$16 ms when a tactor touched the contralateral intact foot, and a JND of 73$\pm$32 ms with stimulation-induced sensation. The JNDs determined for all four participants for both natural touch and stimulation-induced sensation match with values in prior literature.

Our results also demonstrate that the type of tactile stimulus does not impact PSS. The PSS of stimulation-induced sensation was not significantly different than natural tactile sensation. The results of both the stimulation-induced sensation and tactor experiments in the ULA participants match the PSS values in able-bodied individuals (Fujisaki & Nishida, 2009; Takahashi et al., 2008). A similar comparison cannot be made for the LLA participants because, to our knowledge, no previous studies have performed visuotactile SJ tasks on the feet of able-bodied individuals. In agreement with previous temporal synchrony studies (Jaśkowski, 1999; Neumann & Niepel, 2004; Sanford, 1971; David I Shore & Spence, 2005; W. F. Smith, 1933), stronger stimulated intensities caused the PSS to significantly decrease. Such differences support the theory that more intense stimuli are brought to consciousness more quickly (Jaśkowski, 1999; Neumann & Niepel, 2004; Sanford, 1971; David I Shore & Spence, 2005; W. F. Smith, 1933). Though previous studies with natural touch have not identified a definitive impact of stimulus intensity on JND (David I Shore & Spence, 2005), we found that the JND decreased with increased intensity of peripheral nerve stimulation.

This is the first characterization of temporal judgments of electrically-evoked sensations for upper- and lower-limb amputees. The location of touch, i.e. lower-body versus upper-body, did not impact JND. The PSS for stimulation-induced perception was significantly farther from zero for LLA participants than for ULA participants. This difference was likely influenced by conduction velocity. Despite minor differences in electrode technology (C-FINE vs. FINE) among the participants, electrode sizes and the mechanism of nerve excitation remained the same, minimizing the likelihood that the neural interface caused this difference. Afferent sensory information from the foot and hand is carried by Aα and Aβ fibers of similar diameters, which are expected to have similar conduction velocities, and hence, similar information transfer rate to the brain (Kandel et al., 2000). However, the leg is farther from the brain than the arm, resulting in a delay of ~30 ms (Harrar & Harris, 2005). The difference in PSS for stimulation-induced sensation between the ULA participants (from experiments in 2017-2018) and the LLA participants (from the high intensity stimulation vs. vision experiments) was ~38 ms, which matches the difference predicted due to transmission delays.

Stimulation-induced sensation could be delayed by up to 111±62 ms after physical contact without being perceived as incongruent with applied pressure. This delay measure represents an important design consideration when developing sensory neuroprostheses. The rubber hand illusion, which is a strong indicator of potential prosthesis embodiment (Marasco et al., 2011), deteriorates when there is perceived temporal asynchrony between visual and tactile stimuli (Shimada et al., 2009). Therefore, delays larger than this range may disrupt the perception of embodiment and interfere with effective functional prosthesis use. Possible sources of system delay in a sensory neuroprosthesis include signal transmission time and computation time. Neuroprosthesis design should ensure that the total of these system delays does not exceed 111 ms in order to maximize prosthesis embodiment and function.

Additional experience with sensory stimulation and functional context may strengthen the “assumption of unity” between visual stimuli and stimulation-induced sensation. An assumption of unity is thought to govern synchrony perception, and states that the more properties that two stimuli share, the more likely they are to be treated as originating from the same source (Keetels & Vroomen, 2012). The acceptable delay range was larger for participant UL01 than for LL02, though we do not anticipate that this was a result of the level of amputation (below-elbow versus below-knee). Rather, participant UL01 had two additional years of experience with sensory stimulation and had used a closed-loop sensory neuroprosthesis in functional contexts at home (Emily L Graczyk et al., 2018). It is also possible that participant UL01 established a stronger assumption of unity because he could clearly see his prosthetic hand touch the FSR; participant LL02's view of his foot was partially obstructed by his own body. Additionally, pressure on the stump due to foot-floor contact may have affected participant LL02's responses. Though these were limitations, this experiment represented the real-world use of a lower-limb prosthesis.

The results of the functional delay task also provide supporting evidence for a common viewpoint that the brain maintains multisensory synchrony by having a window of temporal integration (meaning that it is insensitive to small time lags) (Keetels & Vroomen, 2012). The way that the brain processes multisensory delays is not yet known, partly because tactile sensation and visual information cannot ordinarily be decoupled. Previous studies have identified frontal, parietal, and subcortical regions that integrate visual and tactile information during the perception of one's own hand (Gentile, Petkova, & Ehrsson, 2010). The insula in particular appears to play a strong role in multisensory synchrony (Bushara, Grafman, & Hallett, 2001).

Although we demonstrated that artificial touch has similar temporal perceptual characteristics to natural touch, our study had certain limitations. Our findings could be more generalizable if they are repeated in a larger group of amputees with more diverse demographics in age, sex, and amputation etiologies. A simultaneity judgment task is used to evaluate perception, but does not quantify how a stimulus is interpreted as closed-loop sensory feedback. Therefore an SJ task cannot evaluate if an additional cognitive load is required once an individual is asked to associate a tactile stimulus with an event. The “synchronous” option in the SJ task may have led participants to assume that the stimuli should belong together, which could have influenced temporal sensitivity (Keetels & Vroomen, 2012). Another constraint was that natural tactile sensation was ramped while stimulation-induced sensation was discrete. To make the natural tactile stimuli as close to discrete as possible, the tactor did not touch the skin before the trial started, and the final position was reached just 22 ms after trial initiation. Because skin compliance varies between people, it is possible that each participant perceived the intensity of the tactor differently. Additionally, although we wished to make comparisons between all stimulus conditions and amputations levels, this comparison may have been limited for upper-limb amputees due to the ~4 year separation between the “tactor vs. vision” and the 2014 “stimulation vs. vision” experiments. Furthermore, though we did not instruct the participants to focus on one stimulus more than the other and we limited trial blocks to less than 15 minutes, the results of visuotactile synchrony tasks can be affected by attention (S. Mattes & Ulrich, 1998; Schneider & Bavelier, 2003; D I Shore, Spence, & Klein, 2001; David I Shore & Spence, 2005; Stelmach & Herdman, 1991; Zampini, Shore, & Spence, 2005). Future tests are also needed to determine how the perception of visuotactile synchrony is modified by more complex functional tasks, such as grasping or walking.

Conclusion

This is the first study to compare the temporal perceptual properties of stimulation-induced sensation to natural tactile sensation, and is also the first to compare upper- and lower-limb amputees with respect to somatosensation evoked in missing limbs. Using peripheral nerve stimulation to evoke somatosensation, we were able to decouple tactile and visual stimuli in a way that is not ordinarily possible, and could therefore evaluate subjective simultaneity in a functional context. Our findings provide important input requirements for prosthesis design and define characteristics of artificial stimulation needed to mimic the naturalistic perception.

CHAPTER 4: Visual inputs and postural manipulations affect the location of somatosensory percepts elicited by electrical stimulation

The following is a copy of the paper "Visual inputs and postural manipulations affect the location of somatosensory percepts elicited by electrical stimulation" published in the journal *Scientific Reports*, Volume 9, on 12 August 2019 (Christie, Charkhkar, et al., 2019).

DOI: https://doi.org/10.1038/s41598-019-47867-1

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Abstract

The perception of somatosensation requires integration of multimodal information, yet the effects of vision and posture on somatosensory percepts elicited by neural stimulation are not well established. In this study, we applied electrical stimulation directly to the residual nerves of trans-tibial amputees to elicit sensations referred to their missing feet. We evaluated the influence of congruent and incongruent visual inputs and postural manipulations on the perceived size and location of stimulation-evoked somatosensory percepts. We found that although standing upright may cause percept size to change, congruent visual inputs and/or body posture resulted in better localization. We also observed visual capture: the location of a somatosensory percept shifted toward a visual input when vision was incongruent with stimulation-induced sensation. Visual capture did not occur when an adopted posture was incongruent with somatosensation. Our results suggest that internal model predictions based on postural manipulations reinforce perceived sensations, but do not alter them. These characterizations of multisensory integration are important for the development of somatosensory-enabled prostheses because current neural stimulation paradigms cannot replicate the afferent signals of natural tactile stimuli. Nevertheless, we found that multisensory inputs can improve perceptual precision and highlight regions of the foot important for balance and locomotion.

Introduction

Over two million people are living with limb loss in the United States (Ziegler-Graham et al., 2008). Commercially available prostheses offer various control mechanisms (manual, body-powered, myoelectric) and multiple degrees of freedom, however none currently provide their users with somatosensory feedback. Previous studies have added sensory feedback via transcutaneous electrical stimulation (S Crea et al., 2015; Dietrich et al., 2012; Geng & Jensen, 2014; Kaczmarek et al., 2000, 1991; Perovic, 2013), vibration (Cipriani et al., 2012; Simona Crea, Edin, Knaepen, Meeusen, & Vitiello, 2017; Kaczmarek et al., 1991; J. A. Sabolich et al., 2002; White et al., 1970), and by directly interfacing with the nerve (Charkhkar et al., 2018; Clippinger et al., 1982; Davis et al., 2012; S Raspopovic et al., 2014; Tan et al., 2014). Adding this feedback can improve functional ability (Dhillon & Horch, 2005; Hebert et al., 2014; Horch et al., 2011; Pylatiuk et al., 2006; Stanisa Raspopovic et al., 2014; Rusaw et al., 2012; J. A. Sabolich et al., 2002; Schiefer et al., 2016; Tan et al., 2014), reduce phantom pain (Dietrich et al., 2012; Tan et al., 2014), and enhance prosthesis embodiment (i.e., incorporation of a prosthesis into one's body schema) (Arzy et al., 2006; Emily L Graczyk et al., 2018; Marasco et al., 2011; Mulvey et al., 2012; Schiefer et al., 2016). It is less clear how such somatosensory feedback integrates with other inputs, such as visual information and body posture, to shape one's perception of the environment. In order to develop maximally beneficial somatosensory neuroprostheses, the impact of these inputs on elicited somatosensory feedback needs to be better understood.

The connection between natural tactile somatosensation and vision is strongly demonstrated in psychophysical and biological studies. Previous psychophysical studies have shown that tactile spatial resolution improves by adding vision (Ernst & Banks, 2002; Kennett et al., 2001; Taylor-Clarke et al., 2004). Electrophysiology experiments have supported these claims: viewing the body modulates human primary somatosensory cortex activity (Schaefer, Heinze, & Rotte, 2005; Taylor-Clarke, Kennett, & Haggard, 2002), and tactile stimulation enhances activity in the visual cortex (Macaluso, Frith, & Driver, 2000). Improvements in tactile acuity occur even when vision of the tactile stimulus is non-informative, i.e., an individual views the body part that is touched but does not see the tactile stimulus itself (Cardini, Longo, & Haggard, 2011; Eads, Lorimer Moseley, & Hillier, 2015; Kennett et al., 2001; Press, Taylor-Clarke, Kennett, & Haggard, 2004; Serino, Padiglioni, Haggard, & Làdavas, 2009; Taylor-Clarke et al., 2004). Tactile and visual feedback are thought to be integrated and inversely weighted by the uncertainty associated with each feedback modality; that is, the modality with greater uncertainty is weighted less (Ernst & Banks, 2002). As long as conditions for visual inputs are favorable, such as when there is sufficient lighting and contrast, uncertainty is typically lower for visual feedback compared to touch, leading to greater trust in visual feedback (Ernst & Banks, 2002). Subsequently, estimates of the environment are more accurate with feedback from both touch and vision than estimates from either modality alone (Ernst & Banks, 2002).

When somatosensory and visual information are spatially incongruent, the parietal cortex is assumed to attempt to reestablish congruency by modulating the “gain” of sensory systems (Ro, Wallace, Hagedorn, Farnè, & Pienkos, 2004). When using mirrors to introduce conflict between the vision of touch and the feeling of touch, tactile sensitivity increases. If transcranial magnetic stimulation is applied to temporarily disengage the posterior parietal cortex, the gaining mechanism is temporarily eliminated. A visible consequence of this corrective gain is the phenomenon of visual capture: when visual and tactile inputs do not occur in the same location, somatosensory percepts can shift towards the location of visual inputs (Pavani, Spence, & Driver, 2000). Once the multimodal mismatch is too large, however, the gaining mechanism is not sufficient and two inputs are no longer perceived as spatially congruent. Despite the well-studied relationship between somatosensation and vision, it is not clear whether the same connection still holds for prostheses with added sensory feedback.

The nervous system also utilizes postural information to determine the location of touch (E Azañón & Soto-Faraco, 2008; Elena Azañón et al., 2015; Heed et al., 2015; Heed & Röder, 2010). Information about the location of a tactile stimulus on the surface of the skin is combined with proprioceptive information about the location of each part of the body (Longo et al., 2015). Most prior studies examined the relationship between posture and tactile localization by asking participants to cross their arms (Heed & Röder, 2010), turn their heads (Ho & Spence, 2007), or shift gaze direction (Medina, Tamè, & Longo, 2018). Posture manipulations that occur during locomotion, such as when the heel strikes the ground, have not been explored with respect to tactile localization.

Additionally, cognitive expectations arise from our internal knowledge of body posture. Prior experiences tell us that while standing upright, we expect to feel our feet touching the ground. These expectations of what we *should* feel influence what we *do* feel (Asai & Kanayama, 2012). This is illustrated by a previous study that measured event-related potentials (ERPs) using electroencephalography (EEG) during a self-generated movement task with human participants. Participants were instructed to move their hand to touch their chest. Before initiating the movement, a task-irrelevant tactile probe was applied to their chest. They found that action preparation modulated tactile probe-evoked somatosensory ERPs (Job, de Fockert, & van Velzen, 2016). Our cognitive expectations largely influence how we perceive reality, which is also demonstrated by illusions resulting from differences between our perception and physical reality. Illusions can achieve a desired perceptual effect by compensating for missing information with the remaining senses (Lederman & Jones, 2011). For example, in one prior study, providing visual information about the stiffness of a virtual spring resulted in reports of haptically feeling physical resistance (Lécuyer, 2009).

To further explore the roles of visual information and posture in tactile localization, we utilized peripheral nerve stimulation (PNS) via implanted nerve cuff electrodes to disassociate multisensory stimuli. We have previously demonstrated that the electrical activation of residual peripheral nerves of trans-tibial amputees can generate somatosensory percepts projected to the missing feet (Charkhkar et al., 2018). In this study, we tested scenarios of congruent and incongruent visual inputs and postural manipulations to determine how multisensory integration affects stimulation-induced somatosensory perception. We hypothesized that changing body position from seated to upright would not impact percept size and location, that congruent information would confine percepts, and that incongruent information would cause percepts to spread. We anticipated that stimulation-induced tactile percepts with locations irrelevant to locomotion (such as tactile sensation on the side of the ankle) could become more functionally relevant as a result of visual inputs and postural manipulations.

Materials and methods

Research participants

Two volunteers with unilateral trans-tibial amputations (LL01 & LL02) due to trauma were enrolled in this study. At the time of device implantation, LL01 was 67 years old and had lost his limb 47 years prior. LL02 was 54 years old and lost his limb nine years beforehand. Both participants were male, regular prosthesis users, and did not have peripheral neuropathy or uncontrolled diabetes. The Louis Stokes Cleveland Veterans Affairs Medical Center Institutional Review Board and Department of the Navy Human Research Protection Program approved all procedures. This study was conducted under an Investigational Device Exemption obtained from the United States Food and Drug Administration. Both participants gave their written informed consent to participate in this study, which was designed in accordance with relevant guidelines and regulations.

Implanted technology and delivery of electrical stimulation

Both participants had 16-contact Composite Flat Interface Nerve Electrodes (C-FINEs) (Freeberg et al., 2017) installed around their sciatic, tibial and/or common peroneal nerves (**Figure 14**) (Charkhkar et al., 2018). The details of implant procedure and post-operative care are described in our prior work (Charkhkar et al., 2018). Both participants received implants in 2016. The described experiments in this study were performed at least one year post-implantation, and participants received electrical stimulation near weekly during other experiments prior to this study. All C-FINE contacts were connected to percutaneous leads that exited the skin on the upper anterior thigh. These percutaneous leads were connected to a custom-designed external stimulator that had a maximum stimulation amplitude of 5.6 mA and a maximum pulse width of 255 µs (Bhadra et al., 2001; B. Smith et al., 1998). Stimulation waveforms were monopolar, asymmetric biphasic, charge-balanced, cathodic-first pulses with return to a common anode placed on the skin above the ipsilateral iliac crest. Stimulation parameters were set in MATLAB (MathWorks, Inc.; Natick, MA, USA) and then sent to a single board computer running xPC Target (MathWorks, Inc.; Natick, MA, USA), which controlled the external stimulator in real time. Stimulation was limited to a charge density of 0.5 $\mu C/mm^2$ in order to minimize the risk of tissue and/or electrode damage (Shannon, 1992).

Figure 14: *Location of nerve cuff electrodes for participants with trans-tibial amputations.*

Three 16-contact C-FINEs were implanted around the sciatic, tibial, and common peroneal nerves of subject LL01 (left) and around the proximal sciatic, distal sciatic, and tibial nerves of subject LL02 (right). Reproduced from Charkhkar *et al*. (Charkhkar et al., 2018), (10.1088/1741-2552/aac964). © IOP Publishing Ltd. CC BY 3.0. Also printed with permission from © *Novie Studio*.

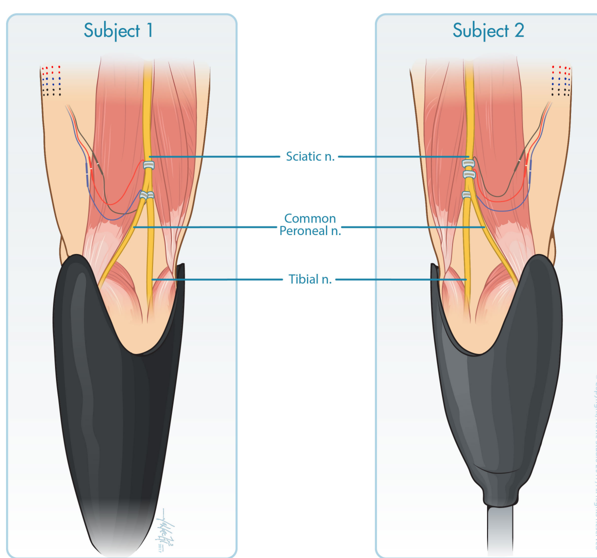


Table 5: Summary of the experimental conditions for testing the effect of visual inputs and postural manipulations on somatosensory percepts.

Electrical stimulation was combined with each condition.

<table>
<tr><th colspan="2">Condition</th><th>Body Position</th><th>Visual Inputs</th><th>Postural Manipulations</th></tr>
<tr><td>#1</td><td>Baseline</td><td>Seated</td><td>None</td><td>None</td></tr>
<tr><td>#2</td><td rowspan="2">Static Standing</td><td rowspan="2">Standing</td><td>None</td><td>None</td></tr>
<tr><td>#3</td><td>Observation of prosthetic foot-floor contact</td><td>None</td></tr>
<tr><td>#4</td><td rowspan="2">Visual input</td><td rowspan="2">Seated</td><td>Observation of experimenter lightly touching the plantar surface of the prosthetic forefoot</td><td>None</td></tr>
<tr><td>#5</td><td>Observation of experimenter lightly touching the plantar surface of the prosthetic rearfoot</td><td>None</td></tr>
<tr><td>#6</td><td rowspan="2">Posture manipulation</td><td rowspan="4">Standing</td><td>None</td><td>Adopting a posture that applies a load on the plantar surface of the prosthetic forefoot</td></tr>
<tr><td>#7</td><td>None</td><td>Adopting a posture that applies a load on the plantar surface of the prosthetic rearfoot</td></tr>
<tr><td>#8</td><td rowspan="2">Visual input + Posture manipulation</td><td>Observation of prosthetic foot-floor contact</td><td>Adopting a posture that applies a load on the plantar surface of the prosthetic forefoot</td></tr>
<tr><td>#9</td><td>Observation of prosthetic foot-floor contact</td><td>Adopting a posture that applies a load on the plantar surface of the prosthetic rearfoot</td></tr>
<tr><td rowspan="2">#S1</td><td rowspan="2">Static Standing, Unloaded, prosthesis off</td><td rowspan="2">Standing with no prosthesis</td><td>None</td><td rowspan="2">None</td></tr>
<tr><td>Eyes open, looking ahead</td></tr>
</table>

Figure 15: *Images of experimental conditions for visual inputs and postural manipulations.*

Postures are demonstrated by participant LL01. The number(s) in the left corner of each photo represent the condition number described in Table 5. The three photos in the bottom row have two numbers because each posture was repeated with the eyes open and closed.

Experimental design

Participants were instructed to adopt a specific posture, as described below, while electrical stimulation was delivered for five consecutive seconds to selected electrode contacts. When stimulation ended, participants drew the location of the elicited percept on a blank diagram of a generic healthy foot. The drawing was captured electronically using a touchscreen display (Cintiq 27QHD Touch; Wacom Co., Kazo, Saitama, Japan).

In the baseline condition, participants sat down and placed the prosthetic foot on a stool such that the knee was fully extended (#1 in Table 5 and **Figure 15**). The dorsal surface of the prosthetic foot was in clear view and the participants were instructed to look at it. In static standing conditions, the participants stood upright with their eyes closed (#2) or with their eyes open and looking down at the prosthesis (#3). When standing upright, there was foot-floor interaction due to weight bearing. While standing upright with the eyes open, there was also visual confirmation of this prosthetic foot-floor contact.

During conditions with added visual inputs, the participants remained seated while watching an experimenter lightly touch the prosthetic plantar forefoot (#4) or rearfoot (#5). The forefoot encompassed the toes and the metatarsals, and the rearfoot encompassed the heel. The experimenter followed real-time visual cues on a computer screen (visible only to the experimenter and not to the participant) to determine the onset and offset for applying touch. The visual cues on the screen were synchronized with the timing of electrical stimulation delivery. The manner of applied physical touch was a mild constant pressure to the bottom of the shoe on the prosthetic foot. The touch was applied such that participants did not feel any added pressure through their socket and could therefore not detect the touch if their eyes were closed. The plantar surface of the foot, where the physical touch was applied, was not visible. This case of non-informative vision was intentional, given that the plantar surface of the foot is typically not visible during locomotion.

During conditions with postural manipulations, the participants stood upright with their eyes closed and adopted a posture that applied a load on either the plantar surface of the prosthetic forefoot (#6) or rearfoot (#7). During conditions with postural manipulations and visual inputs, participants repeated the same postures while looking down at the prosthesis with their eyes open (#8-9). These postural manipulations were designed to approximate stereotypical postures adopted during toe off and heel strike, key phases of gait.

All nine conditions were tested with a total of six C-FINE contacts (three per participant). Suprathreshold electrical stimulation paradigms were chosen after finding sensory detection thresholds via a forced-choice, two-alternative tracking paradigm (Kaernbach, 1990). Pulse width varied by contact from 80-200 μs, pulse amplitude varied between 0.8-1.2 mA, and pulse frequency was set at 20 Hz. The responses evoked by each C-FINE contact were evaluated 15 times per condition, except for one contact with participant LL02 that stopped responding to stimulation due to electrical connection issues unrelated to the experiment. For that contact (R1), we collected at least ten trials per condition. Each experimental session lasted approximately three hours, including time for breaks. Trials were randomized between different electrode contacts in each session. Testing for each contact was typically completed within three sessions, which were 1-6 weeks apart.

After observing differences in the reported percepts during the seated versus static standing conditions, potential causes for these differences were evaluated with additional testing. To evaluate if interactions between electrode contacts and the primary neural fibers activated by electrical stimulation were affected by posture, detection thresholds were collected four times per contact while participants were sitting, and again while they were standing. To determine if changes in percept size were due to the recruitment of additional neural fibers, two contacts were re-tested with a larger electric field induced by delivery of a higher stimulation level while participants were seated. We increased the charge until participants verbally reported the intensity to be double the initially reported level. We also hypothesized that neural fibers do not change their orientations with respect to C-FINE contacts due to changes in body position alone. To evaluate this, we re-tested four contacts while participants stood upright without their prostheses on, while holding onto a walker to maintain stability (condition #S1, Table 5 and **Figure 16**). Finally, we hypothesized that cognitive expectations of foot-floor contact associated with donning the prosthesis affected reported percept size. To test this, each participant reported percept locations while standing on a wooden box with the intact leg and letting the prosthetic leg dangle in the air without contacting the ground (condition #S2, Table 5 and **Figure 16**).

Figure 16: *Images of the supplemental experimental conditions involving standing upright without a prosthesis and standing with the prosthesis unloaded.*

We re-tested contacts F1, F2, R2, and R3 in two supplemental conditions, demonstrated by participant LL01. The number in the top left corner of each photo represents the condition number described in **Figure 15**. When testing contacts F1 and F2, the eyes were open. For contacts R2 and R3, the eyes were closed.

Data analysis

All the collected electronic drawings were processed and analyzed using the Image Processing Toolbox in MATLAB. The toolbox helped to convert drawings into binary mask images, in which pixels for the reported percept areas were set to 1, and all pixels outside the area were set to 0. The foot diagram was divided into three regions of interest (ROIs) that represented the areas most frequently involved in gait and balance: the forefoot, midfoot, and rearfoot. A primary ROI was assigned to each contact. The ROI in which sensations were reported in the greatest number of the baseline trials was identified as the primary ROI.

Inputs collocated with the primary ROI were classified as "congruent." Using the baseline data, the three contacts from participant LL01 were classified as congruent with inputs about the forefoot (referred to as contacts F1-F3) and three from participant LL02 were congruent with inputs about the rearfoot (referred to as contacts R1-R3) (**Figure 17**). In order to test the greatest spatial mismatch, incongruent inputs were applied to the rearfoot when the primary ROI was the forefoot, and vice versa.

In every trial, an activation percentage was assigned to each region of the foot based on how much of the region was covered by the percept drawn by the participant (**Figure 23**). The equation for activation percentage was the following:

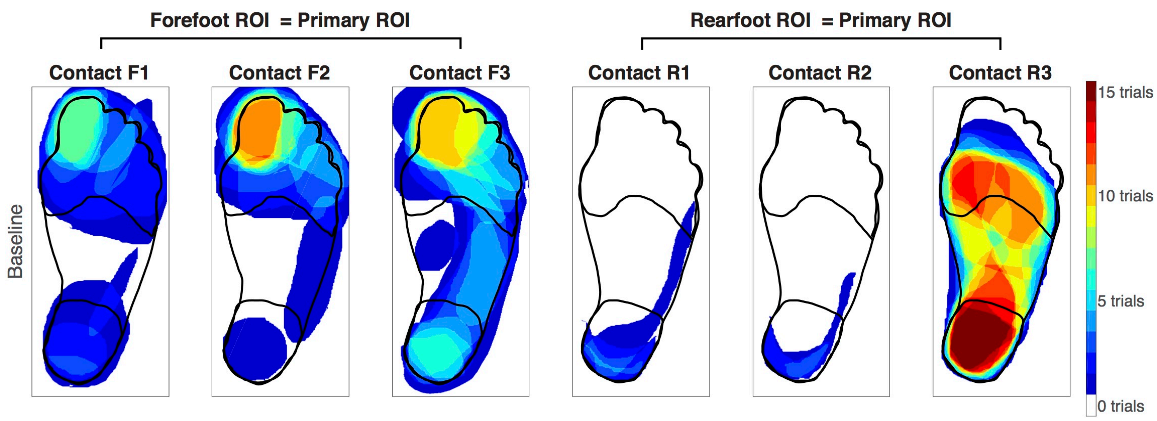
$$Activation\ percentage = 100 \times \frac{area\ of\ percept\ within\ ROI}{area\ of\ ROI}$$

Equation 4

Activation percentages were calculated for the full plantar surface of the foot and each ROI. The mean and standard errors of these activation percentages are given in Table 6.

Figure 17: *Perceived locations of stimulation-induced sensation while participants were seated with no added sensory inputs.*

During the baseline condition, each participant sat with the prosthesis elevated while an electrode contact delivered stimulation to the nerve. They then drew the perceived location of the evoked percept on a blank diagram of the intact foot and leg, represented here as one heat map per contact. Red areas indicate regions that were drawn in all fifteen trials. The forefoot region of interest (ROI) was classified as the primary ROI for contacts F1-F3, and the rearfoot ROI was classified as the primary ROI for contacts R1-R3.



Statistical analyses

Paired t-tests with significance levels of α = 0.05 determined if the activation percentages in one condition were significantly different than the baseline condition. We split the electrode contacts into two groups based on their primary ROIs, therefore we grouped the forefoot contacts (F1, F2, F3) and rearfoot contacts (R1, R2, R3) together during statistical analyses. We compared the primary ROI between conditions and a combination of the two remaining ROIs (referred to later as 'regions outside of the primary ROI') between conditions.

During the comparisons of sitting versus static standing (conditions #2, #3, #S1, #S2), we analyzed the activation of the whole plantar foot surface because we did not add inputs to specific ROIs. Moreover, two-tailed tests were performed because we hypothesized that there would be no significant changes in percept size. In all congruent and incongruent conditions (#4-9), one-tailed t-tests were used to reflect our hypotheses that congruent information localizes percepts, and incongruent information causes percepts to spread. A one-way repeated measures analysis of variance (ANOVA) was used to compare the sensory detection thresholds between sitting and standing for all electrode contacts.

Results

Perceptual differences between sitting and static standing

With respect to the baseline condition, activation in the entire plantar surface of the foot was significantly different during static standing (**Figure 18**). Somatosensory percepts evoked by rearfoot contacts were different when the eyes were closed (condition #2, $p=0.031$) and the percepts evoked by forefoot contacts were different when the eyes were open (condition #3, $p<0.001$). For the rearfoot contacts, activation in the plantar surface of the foot decreased by $4\pm2\%$. For the forefoot contacts, activation in the plantar foot surface increased by $20\pm5\%$.

While participants stood upright without wearing their prostheses (condition #S1), only percepts evoked by rearfoot contacts were significantly different than the baseline condition ($p=0.013$, **Figure 19**a). In a post hoc two-tailed t-test that ungrouped the rearfoot contacts, there was no significant difference in activation percentage for contact R2 with respect to the baseline; the baseline percentage was $1\pm1\%$ and the condition #S1 percentage was $0\pm0\%$. Therefore, while standing with the prosthesis off, the statistical effect for the rearfoot contacts was largely dominated by contact R3. While participants stood upright but did not load their prostheses on the ground (condition #S2), both groups of electrode contacts evoked significantly different percepts in the plantar surface of the foot (**Figure 19**b) (p=0.021 for the forefoot contacts, p=0.004 for the rearfoot contacts). Activation percentages in the plantar surface of the foot increased for contacts F1, F2, and R3 and decreased for contact R2.

Figure 18: *Perceived locations of stimulation-induced sensation while participants stood upright.*

A generic healthy foot is outlined in grey. Shaded red areas indicate regions that were reported more than the baseline seated condition, and shaded blue regions represent a decrease in reporting compared to baseline. † indicates significant changes in percept reporting frequency and/or percept size over the entire plantar surface of the foot (two-tailed paired t-tests, $p<0.05$). **(a)** Stimulation was delivered while participants stood upright with their eyes closed. **(b)** Stimulation was delivered while participants stood upright with their eyes open, looking down at their feet.

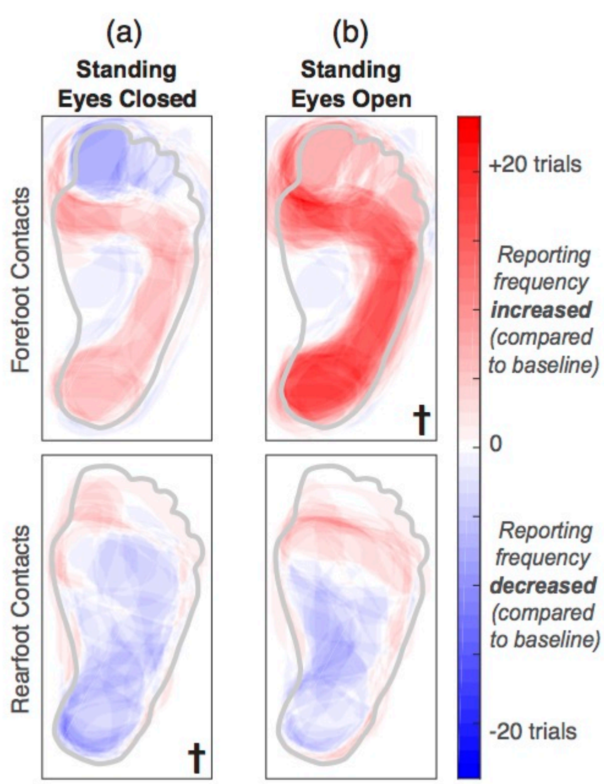


Figure 19: *Perceived locations of stimulation-induced sensation while participants stood upright without a prosthesis or with the prosthesis unloaded.*

A generic healthy foot is outlined in grey. Shaded red areas indicate regions that were reported more than the baseline seated condition, and shaded blue regions represent a decrease in reporting compared to baseline. † indicates significant changes in percept reporting frequency and/or percept size over the entire plantar surface of the foot (two-tailed paired t-tests, $p<0.05$). We re-tested contacts F1, F2, R2, and R3 in two supplemental conditions. When testing contacts F1 and F2, the eyes were open in all three conditions shown here. For contacts R2 and R3, the eyes were closed. **(a)** During the "prosthesis off" condition, electrical stimulation was delivered while a participant stood upright without wearing their prostheses. **(b)** During the "prosthesis unloaded" condition, electrical stimulation was delivered while a participant stood on a wooden box with the intact leg and let the prosthetic leg dangle in the air. **(c)** Electrical stimulation was delivered while participants stood upright with their prostheses loaded. These results are also shown in **Figure 18** but repeated here to easily identify perceptual differences between standing conditions.

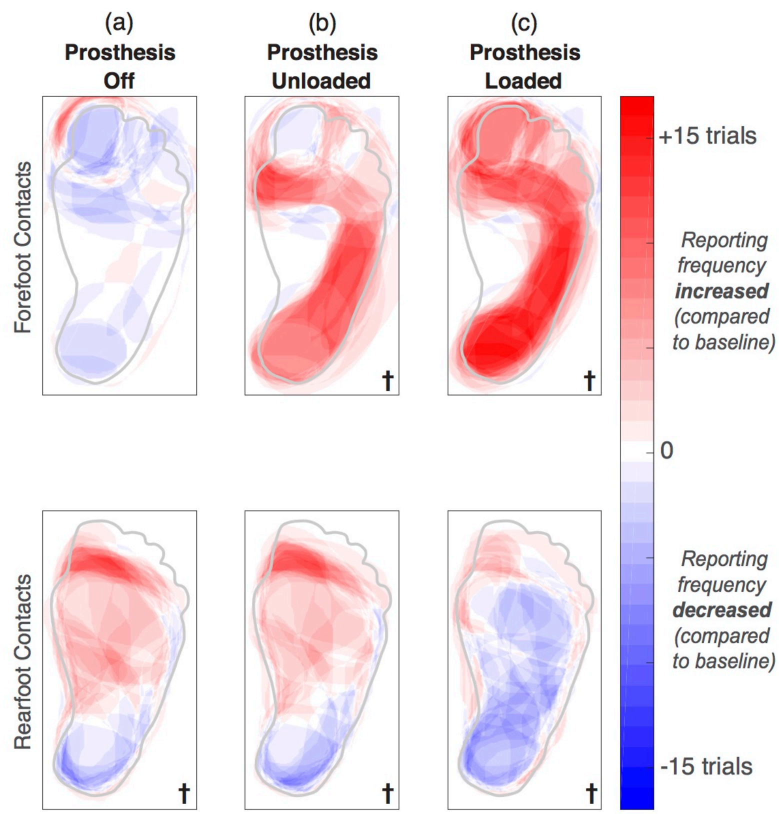
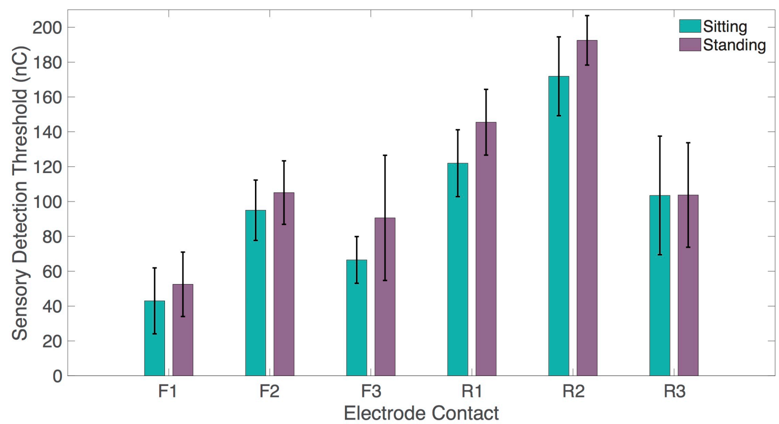


Figure 20: *Charge thresholds while sitting versus standing.*

Sensory detection thresholds while participants sat down with their prostheses elevated (teal) or stood upright with their eyes open (purple). N=4 trials per contact per posture.



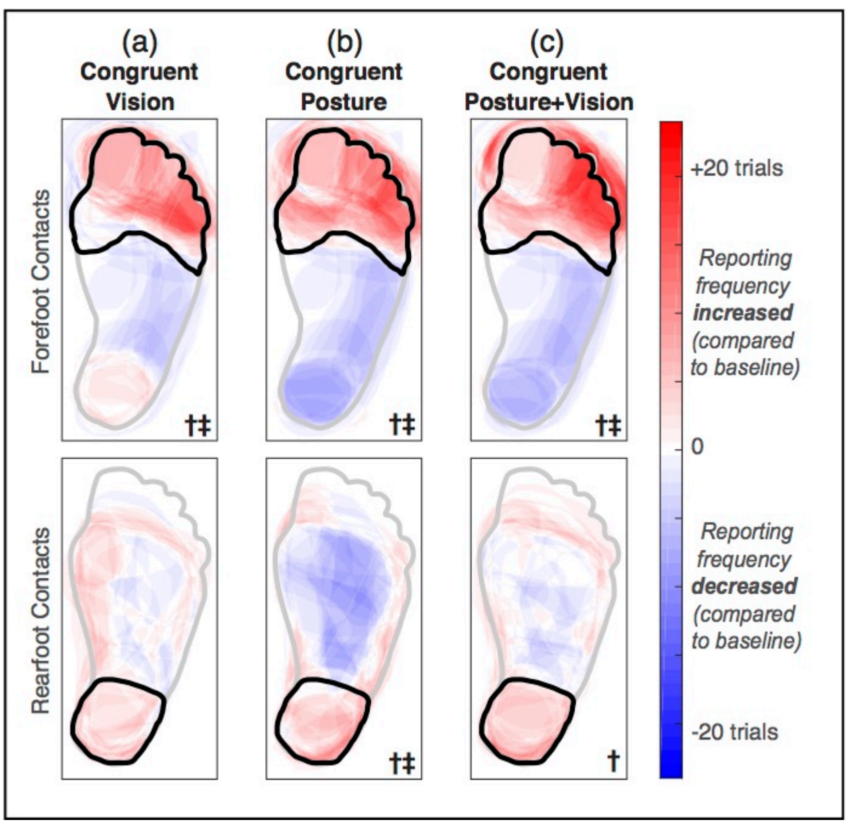
Sensory detection thresholds were not significantly different between sitting and standing. Average thresholds across all six contacts were 100±45 nC while sitting and 115±48 nC while standing (**Figure 20**). We re-tested contacts F1 and F2 at a higher charge level and did not find a significant increase in percept area on the plantar foot surface (**Figure 24**).

Perception during congruent inputs

The addition of congruent visual inputs (conditions #4 and #5) caused more localized percepts than the baseline condition for the group of forefoot contacts (**Figure 21**a). Reports of percepts in the primary ROI increased in frequency and/or grew to cover more of the ROI (p=0.003). Although electrical stimulation paired with congruent visual inputs led to increased activation of the primary ROI for the rearfoot contacts, the effect was not strong enough to have statistical significance (p=0.066). For rearfoot contacts R1 and R2, the baseline percepts were primarily located on the side of the ankle with a few percepts reported on the heel. It is possible that the perception of percepts on the ankle overrode the percepts on the heel, interfering with the ability of visual inputs applied to the heel to act as "congruent" with electrical stimulation.

Figure 21: *Perceived locations of stimulation-induced sensation when congruent visual inputs and/or postural manipulations are involved.*

A generic healthy foot is outlined in grey, and the location of an added input is outlined in black. "Congruent" signifies that the experimenter touched the location of the primary ROI. The forefoot contacts (F1-F3) had a primary ROI in the forefoot, and rearfoot contacts (R1-R3) had a primary ROI in the rearfoot. Shaded red areas indicate regions that were reported more than the baseline seated condition, and shaded blue regions represent a decrease in reporting compared to baseline. † denotes significantly increased activation in the primary ROI, and ‡ indicates significantly decreased activation in regions outside of the primary ROI (one-tailed paired t-tests, $p<0.05$). **(a)** During the conditions involving congruent visual inputs, electrical stimulation was delivered while participants sat and watched an experimenter apply a light touch to the primary ROI on the plantar surface of the prosthesis. **(b)** During conditions involving congruent postural manipulations with the eyes closed, electrical stimulation was delivered while participants stood upright and adopted a posture that applied a load to the location of the primary ROI. **(c)** Repeated condition *'b'* with the eyes open.



The addition of congruent postural manipulations (conditions #6 and #7) caused more localized percepts than the baseline condition for both groups of electrode contacts (**Figure 21**b). Primary ROI activation increased (p=0.004 for forefoot contacts and p=0.046 for rearfoot contacts) and activation outside of the primary ROI decreased (p=0.003 for forefoot contacts and p=0.013 for rearfoot contacts).

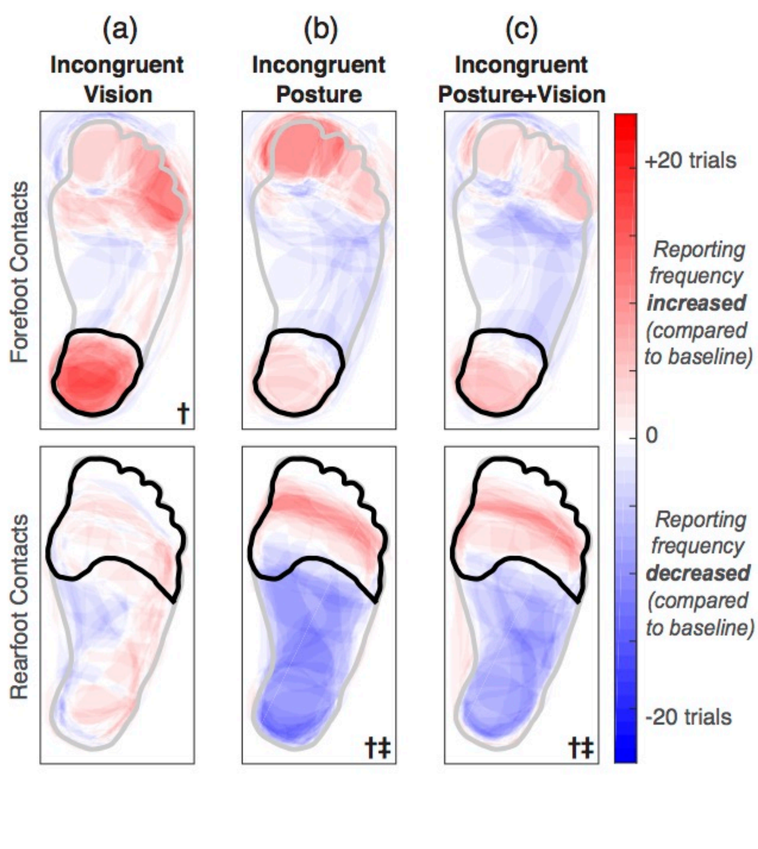
During conditions with congruent visual inputs and postural manipulations (#8 and #9), percepts were more localized than the baseline condition for both groups of electrode contacts (**Figure 21**c). Primary ROI activation increased for both groups of contacts (p=0.006 for forefoot contacts and p=0.035 for rearfoot contacts) and activation outside of the primary ROI decreased for the forefoot contacts (p=0.005).

Perception during incongruent inputs

Incongruent visual inputs (conditions #4 and #5) led to an increase in activation in the ROI touched by the experimenter, which was outside of the primary ROI, for the forefoot electrode contacts only (p=0.027, **Figure 22**a). Conversely, incongruent postural manipulations produced a decrease in primary ROI activation in the rearfoot electrode contacts (**Figure 22**b,c). This occurred in both the eyes closed (p=0.001, conditions #6 and #7) and eyes open (p=0.004, #8 and #9) conditions. Additional post hoc t-tests confirmed that this effect was again dominated by electrode contact R3. Contacts R1 and R2 did not evoke significantly different percepts between baseline and incongruent postural manipulation conditions, but contact R3 did (eyes closed p<0.001, eyes open p=0.003). The primary ROI for contact R3 was classified as the rearfoot from baseline data, but the entire plantar surface of the foot was frequently reported (parts of the forefoot ROI were reported in 41±5% of trials, compared to 84±2% for the rearfoot, which was the primary ROI). Though there were significant differences, they may not have been the result of truly "incongruent" inputs, but rather postural manipulations helping to focus attention on an alternate region that had fewer reported percepts than the primary ROI in the baseline condition.

Figure 22: *Perceived locations of stimulation-induced sensation when incongruent visual inputs and/or postural manipulations are involved.*

A generic healthy foot is outlined in grey, and the location of an added tactile input is outlined in black. "Incongruent" signifies that the experimenter touched a location outside of the primary ROI (forefoot contacts had a primary ROI in the forefoot, and rearfoot contacts had a primary ROI in the rearfoot). Shaded red areas indicate regions that were reported more than the baseline seated condition, and shaded blue regions represent a decrease in reporting compared to baseline. † denotes significantly increased activation in regions outside of the primary ROI, and ‡ indicates significantly decreased activation in the primary ROI (one-tailed paired t-tests, $p<0.05$). **(a)** During the conditions involving incongruent visual inputs, electrical stimulation was delivered while participants sat and watched an experimenter apply a light touch to a region outside of the primary ROI. **(b)** During conditions involving incongruent postural manipulations with the eyes closed, electrical stimulation was delivered while participants stood upright and adopted a posture that applied a load away from the location of the primary ROI. **(c)** Repeated condition *'b'* with the eyes open.



Discussion

Humans integrate multiple streams of information to develop an internal understanding of the external environment and their interactions with it (Choi, Lee, & Lee, 2018; Driver & Noesselt, 2008; Harris et al., 2015). Information from one sensory stream can affect perception of information from another, helping to reinforce or redefine ambiguous information (Driver & Noesselt, 2008; Guerraz et al., 2012). In this study, we evaluated the perception of touch size and location by selectively manipulating the interplay between afferent somatosensory information, body posture, and vision.

Expectations of foot-floor contact can impact the size of somatosensory percepts

Static standing affected percept location with respect to the baseline condition. While standing, percepts covered a smaller percentage of the foot surface for rearfoot contacts, and a larger percentage for forefoot contacts. These changes were most likely not due to any changes in nerve fiber recruitment. Sensory detection thresholds were not found to be significantly different between sitting and standing, which indicates recruited neural fibers did not move towards or away from the tested C-FINE contacts. However, it was still possible that the transition from sitting to standing would change the nerve cross-sectional geometry and consequently result in recruitment of additional fibers. To address this, while participants were seated, we increased the delivered charge density to broaden the electric field and recruit any smaller nearby fibers. However, we found that percept size on the plantar surface of the foot did not significantly increase in response to the elevated charge density, suggesting that increases in percept size while standing were not due to additional fiber recruitment. One limitation of this test is that we may not have increased charge enough to see an effect. However, increasing charge levels any further caused discomfort to the participant.

While standing without wearing the prosthesis, there were few differences in percept size compared to a seated position, indicating that simply changing body position did not affect fiber recruitment. While stimulation through one contact (R3) elicited a significant increase in percept area, percepts evoked by the same contact covered over half of the plantar surface of the foot during the baseline condition. Therefore, this contact may have been close to multiple fibers of a similar diameter, and even small changes in posture could have realigned nearby fibers and affected recruitment. In contrast, donning the prosthesis but keeping it unloaded while standing affected percepts evoked by both groups of electrode contacts. We suspect that this was a result of the individuals' internal knowledge of limb length (length of the residual leg plus the prosthesis) and expectations of potential foot-floor contact while wearing the prosthesis.

Percepts were focused by congruent information

Our results confirmed that the addition of at least one congruent source of information helped participants clarify the location of stimulation-induced somatosensory percepts. Though previous studies have shown that cognitive expectations influence tactile acuity (Asai & Kanayama, 2012), the effects of postural manipulations were not well established. We found that postural manipulations, which are accompanied by an intrinsic understanding of the expected consequences of those manipulations, caused an increase in tactile sensitivity with respect to baseline. Though the addition of visual information localized stimulation-induced sensory percepts, just as natural somatosensation can (Kennett et al., 2001; Taylor-Clarke et al., 2004), congruent postural manipulations had an even stronger effect.

Each form of congruent inputs was likely assisted by directing participants' attention to the primary ROI. Previous studies on natural somatosensation have found that sustained spatial attention to one region of the body results in enhanced processing of tactile stimuli in that region over unattended regions (Sambo & Forster, 2011). For the case of tactile sensations elicited by electrical stimulation, attending to the primary ROI may have made it easier for participants to identify percepts in that location and to ignore percepts that occurred in unattended regions.

The results of the congruent scenarios tested with PNS could relax certain constraints in the implementation of somatosensory feedback in prostheses. Malleable percepts in functionally relevant locations can improve the fidelity and perhaps the ultimate utility of sensory neuroprostheses in locomotion. When developing sensory neuroprostheses, amputees who lost their limbs many years ago may have some initial trouble visualizing restored limb sensation and identifying the locations of evoked percepts. Although the brain representation of a missing limb is maintained over many years (Wesselink et al., 2019), we have found that there appears to be an acclimation period between the first-ever percept elicited by PNS and the ability to express a clear and consistent percept referred to a missing body part (Charkhkar et al., 2018). We hypothesize that individuals receiving somatosensory neuroprostheses would likely benefit from a protocol applying congruent inputs to help localize percepts to functionally relevant locations and accelerate this acclimation process. This is analogous to how previous studies have exploited natural sensory illusions to achieve a desired perceptual effect by compensating for missing details (Lederman & Jones, 2011).

Visual capture occurred for congruent and incongruent visual inputs

While congruent visual information localized the area of perceived touch, incongruent visual information broadened the location of the perceived touch for the forefoot contacts. Our findings corroborate prior reports on visual capture with natural somatosensation (Pavani et al., 2000): the location of stimulation-induced somatosensory percepts was affected by the location of visual inputs. Similar to past studies, for the rearfoot contact group, we found that if the mismatch between two inputs was too great, the illusion of congruency was not reached (B. Stein & Meredith, 1993) and perceived touch did not shift to include the location where touch was observed. Specifically, if plantar regions outside of the primary ROI were never reported in the baseline condition (i.e., the midfoot or forefoot for contacts R1 and R2), the perceived touch could not be shifted to these areas. It is also possible that visual capture could have occurred if the spatial mismatch was not as large between the visual input and stimulation-induced somatosensation (B. Stein & Meredith, 1993). An alternative explanation for our observations with incongruent visual inputs is that they were not completely incongruent. For example, for all three forefoot contacts, percepts were reported outside of the primary ROI in at least one of 15 baseline trials. Visual inputs likely directed the participants' attention to percepts that were less perceptible during the baseline condition, enhancing them by attending to that location (Sambo & Forster, 2011). These results provide further evidence of a gaining system for establishing multisensory congruency (Ro et al., 2004).

In subsequent studies, our protocol for disassociating somatosensation from other stimuli could provide a unique framework to examine which regions of the brain are involved in re-establishing congruency between two inputs.

When incongruent with somatosensation, postural manipulations prevented visual capture

Postural manipulations have a gating effect on the ability of visual information to influence the perceived location of stimulation-induced somatosensation. Although observed during conditions with incongruent visual inputs, visual capture did not occur for the majority of contacts when incongruent postural manipulations were also present. Though all experimental conditions involved static postures, a movement command had to be executed in order to adopt each posture. An internal copy of this motor command, called an efference copy, accompanies self-generated movement. An efference copy is then used to create an internal prediction of the movement's sensory consequences (Gibson, 1962; Pavani et al., 2000). When there is a discrepancy between the predicted and actual sensory information, an internal prediction model is updated (Magee & Kennedy, 1980). Even when these sensory predictions were isolated from vision during conditions #6 and #7, incongruent postural manipulations still did not modulate stimulation-induced percepts for the majority of contacts. Combined with our observations on congruent postural manipulations, this suggests that expectations based on motor commands can reinforce the location of perceived sensations, but not alter location.

Previous work also hypothesizes that visual capture only occurs if a seen posture is proprioceptively feasible (Pavani et al., 2000). Moreover, visual capture of touch occurs for body image (how one's own body is perceived), but not as strongly for body schema (which is involved in self-generated actions) (Kammers, de Vignemont, Verhagen, & Dijkerman, 2009; Pitron & de Vignemont, 2017). It is possible that body schema is not as heavily influenced by visual capture due to the involvement of proprioceptive information (Job et al., 2016; Kammers et al., 2009). The postural manipulations in this study incorporated proprioceptive information from the residual limb, which likely influenced visual capture. If the mismatch between postural manipulations and visual inputs had been less drastic, visual capture may have occurred. It would be interesting to investigate if these observations also occur during active movements combined with visual inputs and electrical stimulation.

In future studies, it would be informative to apply incongruent inputs at different locations around the leg to test the sensitivity of visual capture. The primary somatosensory cortex (S1) is somatotopically organized with a layout that broadly follows the layout of the body itself. The foot region of S1 neighbors the toe and leg regions of S1 (Penfield & Boldrey, 1937). A previous study found that visual capture of touch occurs in accordance with the somatotopic organization of S1 (Serino et al., 2009). While participants viewed the hand, tactile discrimination thresholds improved on the hand and the face, but not the foot. The hand and face regions border each other in the somatosensory homunculus, but multiple regions separate the hand from the foot. It would be interesting to identify when visual capture is disrupted with respect to the distance between two regions of the body and somatosensory homunculus.

In a survey on phantom limb pain, 80% of amputees reported that they had experienced phantom pain over a four-week period prior to the survey (Ephraim, Wegener, MacKenzie, Dillingham, & Pezzin, 2005). The exact cause of phantom limb pain is not yet well defined. One previous study suggests that phantom pain is the result of incongruence between an efference copy and afferent sensory information (McCabe, Haigh, Halligan, & Blake, 2005), whereas other studies could not establish this link (G. L. Moseley & Gandevia, 2005; G. Lorimer Moseley, 2006; Wand et al., 2014). Incongruent conditions in this study did not induce any pain in our participants.

Study design limitations

Although we used a unique experimental design to evaluate the effects of congruent and incongruent inputs on somatosensation, our study had certain limitations. Our findings could become more generalized if they are repeated in a larger group of amputees with more diverse demographics in age, sex, and amputation etiologies. At the time of this study, both participants received electrical stimulation-induced somatosensation in the laboratory for over a year and had a clear phantom perception of their missing limbs. They perceived electrical stimulation-elicited sensations as originating from their missing limbs, which was different from their general phantom perception. Future studies with a larger sample size could determine how stimulation-induced sensation is affected by the anomalies in phantom perception.

We did not expect significant variability in percept location between sessions because previous work has demonstrated that somatosensory percepts evoked by nerve cuff electrodes in amputees remain stable over the course of five months (Charkhkar et al., 2018). However, some trial-to-trial variability in reported percept location can be expected. For example, able-bodied individuals had an average localization error of 11.7$\pm$2.3 mm when reporting the location of a physical tactile stimulus applied to the foot (Franz, 1913). Tactile localization variability can be caused by a number of things, such as the attentional state of the participant (Braun et al., 2005). Such variability would be random, however, rather than systematic like the changes in location we observed in the present study.

Additionally, the exact timing between stimulation-induced sensation and physically applied touch likely had some variation due to the experimenter's response time and movement planning. However, this delay was minimal compared to the length of stimulation-induced sensation. Human response time and movement planning is typically about 262 ms (Barthelemy & Boulinguez, 2001), more than an order of magnitude smaller than the length of stimulation-induced sensation.

Conclusion

Using peripheral nerve stimulation to evoke somatosensory percepts, we developed an experimental design that isolated afferent somatosensory information, postural manipulations, and vision. Using this disassociation method, visual inputs and postural manipulations were either congruent or incongruent with stimulation-elicited somatosensation. We found that standing upright may cause changes in percept area due to the cognitive expectations of weight bearing and foot-floor contact. Percepts could be focused by congruent visual inputs and/or congruent postural manipulations. We also demonstrated that visual capture occurred when visual information was incongruent with stimulation-induced sensation, which matches previous studies with natural somatosensation (Pavani et al., 2000). When incongruent with somatosensation, postural manipulations prevented visual capture. Furthermore, our results suggest that expectations based on motor commands can reinforce the location of perceived sensations, but not alter them.

These characterizations of multisensory integration are important for somatosensory prosthesis development because current neural stimulation paradigms can only approximate the afferent signals from natural tactile stimuli. Our results suggest that the redundancy of multisensory inputs can improve perceptual precision and provide feedback in regions of the foot that are important for balance and locomotion.

Supplemental information

Figure 23: *Activation percentage calculation.*

An image of the plantar surface of the foot was divided into three regions of interest (ROIs): forefoot (outlined in teal), midfoot (outlined in orange), and rearfoot (outlined in purple). For each trial, an activation percentage was calculated for each ROI. In the example below, representative opaque blue percepts are drawn in the forefoot and rearfoot ROIs. Assuming this is contact #1, condition #1, and trial #1, the activation percentage of the forefoot ROI is 20%, midfoot ROI activation=0%, and rearfoot ROI activation=40%.

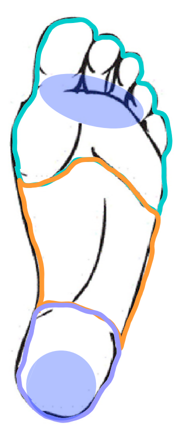


***Figure 24:** Increased charge while sitting.*

A generic healthy foot and each region of interest are outlined in grey. Shaded red areas indicate regions that were reported more than the baseline seated condition, and shaded blue regions represent a decrease in reporting compared to baseline. **(a)** Contacts F1 and F2 were re-tested at increased charge levels while participants remained seated. There were no significant increases compared to the baseline seated condition. **(b)** Stimulation was delivered while participants stood upright with their eyes open, at the same charge levels as the baseline condition. These results are also shown in **Figure 18**, but repeated here to easily identify perceptual differences between increasing the charge and standing upright.

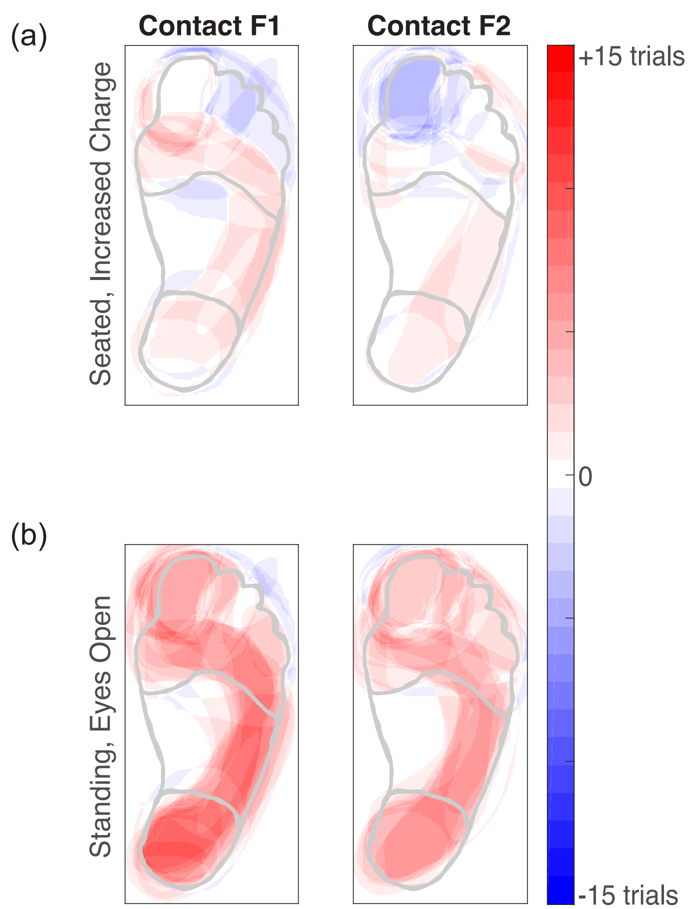


Table 6: Activation percentages.

Experimental condition numbers from Table 5 are included in the top row. Activation percentages are listed for the full plantar surface of the foot ('Full foot') and the three regions of interest: forefoot (Fore'), midfoot (Mid'), and rearfoot (Rear'). The 'forefoot contacts' row lists the average of all forefoot contacts tested in each condition. The 'rearfoot contacts' row displays the average of all rearfoot contacts. For conditions #S1 and #S2, only contacts F1, F2, R2, and R3 were tested.

	Contact F1	Contact F2	Contact F3	Forefoot contacts	Contact R1	Contact R2	Contact R3	Rearfoot contacts
Baseline (#1)	Fore: 24±9% Mid: 4±3% Rear: 12±7% Full foot: 15±6%	Fore: 36±6% Mid: 3±2% Rear: 5±4% Full foot: 18±3%	Fore: 39±8% Mid: 15±6% Rear: 28±9% Full foot: 28±6%	Fore: 33±4% Mid: 7±2% Rear: 15±4% Full foot: 20±3%	Fore: 0±0% Mid: 1±1% Rear: 12±6% Full foot: 3±2%	Fore: 0±0% Mid: 0±0% Rear: 5±3% Full foot: 1±1%	Fore: 41±5% Mid: 61±6% Rear: 84±2% Full foot: 57±4%	Fore: 15±4% Mid: 23±5% Rear: 36±6% Full foot: 22±4%
Standing, eyes closed (#2)	Fore: 36±10% Mid: 7±4% Rear: 16±9% Full foot: 22±7%	Fore: 30±10% Mid: 13±5% Rear: 26±10% Full foot: 23±7%	Fore: 34±9% Mid: 12±5% Rear: 34±10% Full foot: 26±7%	Fore: 33±5% Mid: 11±3% Rear: 26±6% Full foot: 23±4%	Fore: 0±0% Mid: 1±1% Rear: 5±5% Full foot: 2±2%	Fore: 0±0% Mid: 2±1% Rear: 18±8% Full foot: 4±2%	Fore: 41±5% Mid: 41±5% Rear: 45±11% Full foot: 42±4%	Fore: 15±4% Mid: 16±3% Rear: 24±6% Full foot: 17±3%
Standing, eyes open (#3)	Fore: 53±7% Mid: 25±6% Rear: 60±9% Full foot: 44±6%	Fore: 58±8% Mid: 20±6% Rear: 39±11% Full foot: 40±7%	Fore: 50±9% Mid: 18±6% Rear: 43±11% Full foot: 37±7%	Fore: 54±5% Mid: 21±3% Rear: 47±6% Full foot: 40±4%	Fore: 1±1% Mid: 1±1% Rear: 8±8% Full foot: 3±3%	Fore: 3±3% Mid: 2±2% Rear: 16±7% Full foot: 5±3%	Fore: 50±4% Mid: 42±6% Rear: 62±9% Full foot: 49±4%	Fore: 19±4% Mid: 16±4% Rear: 30±6% Full foot: 20±4%
Standing, prosthesis off (#S1)	Fore: 24±7% Mid: 4±4% Rear: 6±6% Full foot: 13±5%	Fore: 24±6% Mid: 0±0% Rear: 0±0% Full foot: 11±3%		Fore: 24±5% Mid: 2±2% Rear: 3±3% Full foot: 12±3%		Fore: 0±0% Mid: 0±0% Rear: 0±0% Full foot: 0±0%	Fore: 63±2% Mid: 80±3% Rear: 74±7% Full foot: 71±2%	Fore: 32±6% Mid: 40±8% Rear: 37±8% Full foot: 36±7%
Standing, prosthesis unloaded (#S2)	Fore: 52±9% Mid: 21±6% Rear: 43±12% Full foot: 39±8%	Fore: 33±8% Mid: 16±5% Rear: 26±11% Full foot: 25±7%		Fore: 42±6% Mid: 19±4% Rear: 35±8% Full foot: 32±5%		Fore: 0±0% Mid: 0±0% Rear: 0±0% Full foot: 0±0%	Fore: 64±2% Mid: 75±5% Rear: 71±7% Full foot: 69±3%	Fore: 32±6% Mid: 37±7% Rear: 36±7% Full foot: 34±7%
Congruent visual inputs (#4 forefoot contacts, #5 rearfoot contacts)	Fore: 47±7% Mid: 1±1% Rear: 5±5% Full foot: 22±3%	Fore: 48±7% Mid: 3±2% Rear: 18±8% Full foot: 25±4%	Fore: 48±7% Mid: 1±1% Rear: 26±9% Full foot: 26±3%	Fore: 47±4% Mid: 2±1% Rear: 16±5% Full foot: 25±2%	Fore: 2±2% Mid: 8±6% Rear: 21±7% Full foot: 8±4%	Fore: 4±4% Mid: 8±6% Rear: 22±8% Full foot: 9±5%	Fore: 42±6% Mid: 49±6% Rear: 79±6% Full foot: 52±5%	Fore: 17±4% Mid: 23±5% Rear: 42±6% Full foot: 24±4%
Congruent postural manipulations, without vision (#6 forefoot contacts, #7 rearfoot contacts)	Fore: 58±6% Mid: 2±1% Rear: 0±0% Full foot: 26±3%	Fore: 49±7% Mid: 0±0% Rear: 0±0% Full foot: 21±3%	Fore: 43±7% Mid: 2±1% Rear: 6±5% Full foot: 20±4%	Fore: 50±4% Mid: 1±0% Rear: 2±2% Full foot: 23±2%	Fore: 1±1% Mid: 3±2% Rear: 11±5% Full foot: 4±2%	Fore: 1±1% Mid: 4±2% Rear: 37±11% Full foot: 9±3%	Fore: 28±5% Mid: 35±7% Rear: 79±4% Full foot: 40±4%	Fore: 10±3% Mid: 15±3% Rear: 44±6% Full foot: 19±3%
Congruent postural manipulations, with vision (#8 forefoot contacts, #9 rearfoot contacts)	Fore: 45±7% Mid: 0±0% Rear: 0±0% Full foot: 20±3%	Fore: 57±8% Mid: 1±1% Rear: 11±6% Full foot: 28±4%	Fore: 46±7% Mid: 3±1% Rear: 0±0% Full foot: 21±3%	Fore: 49±4% Mid: 1±0% Rear: 4±2% Full foot: 23±2%	Fore: 0±0% Mid: 1±1% Rear: 13±9% Full foot: 3±2%	Fore: 2±2% Mid: 8±5% Rear: 39±10% Full foot: 12±4%	Fore: 43±5% Mid: 48±8% Rear: 79±6% Full foot: 52±5%	Fore: 17±4% Mid: 21±5% Rear: 48±6% Full foot: 25±4%
Incongruent visual inputs (#5 forefoot contacts, #4 rearfoot contacts)	Fore: 39±8% Mid: 4±2% Rear: 38±9% Full foot: 26±5%	Fore: 55±8% Mid: 10±4% Rear: 42±10% Full foot: 36±5%	Fore: 36±6% Mid: 6±4% Rear: 38±10% Full foot: 25±4%	Fore: 43±4% Mid: 6±2% Rear: 39±6% Full foot: 29±3%	Fore: 3±2% Mid: 5±4% Rear: 16±6% Full foot: 6±3%	Fore: 1±1% Mid: 6±4% Rear: 13±7% Full foot: 5±3%	Fore: 42±5% Mid: 51±7% Rear: 78±3% Full foot: 52±4%	Fore: 17±4% Mid: 22±5% Rear: 37±6% Full foot: 23±4%
Incongruent postural manipulations, without vision (#7 forefoot contacts, #6 rearfoot contacts)	Fore: 48±6% Mid: 4±3% Rear: 24±10% Full foot: 27±2%	Fore: 33±5% Mid: 0±0% Rear: 12±7% Full foot: 17±2%	Fore: 38±7% Mid: 5±3% Rear: 21±8% Full foot: 23±4%	Fore: 40±3% Mid: 3±1% Rear: 19±5% Full foot: 22±2%	Fore: 0±0% Mid: 1±1% Rear: 3±2% Full foot: 1±1%	Fore: 2±2% Mid: 1±1% Rear: 10±7% Full foot: 3±2%	Fore: 54±4% Mid: 12±3% Rear: 27±10% Full foot: 33±3%	Fore: 21±4% Mid: 5±1% Rear: 14±5% Full foot: 13±3%
Incongruent postural manipulations, with vision (#9 forefoot contacts, #8 rearfoot contacts)	Fore: 29±8% Mid: 0±0% Rear: 16±7% Full foot: 16±3%	Fore: 31±6% Mid: 0±0% Rear: 14±8% Full foot: 16±3%	Fore: 41±7% Mid: 7±5% Rear: 35±9% Full foot: 27±5%	Fore: 34±4% Mid: 2±2% Rear: 21±5% Full foot: 20±2%	Fore: 2±2% Mid: 1±1% Rear: 8±6% Full foot: 3±1%	Fore: 2±2% Mid: 0±0% Rear: 2±2% Full foot: 1±1%	Fore: 55±4% Mid: 26±5% Rear: 47±11% Full foot: 42±4%	Fore: 22±4% Mid: 10±3% Rear: 20±5% Full foot: 17±3%

Table 7: Statistical results for standing conditions.

The p-values and 95% confidence intervals of all t-tests performed on standing conditions are listed below. Blue text indicates significant perceptual changes ($p \leq 0.05$). Two-tailed t-tests were performed on the full plantar surface of the foot only, not individual ROIs. The lower and upper boundaries of the confidence intervals are in parentheses.

	Standing Eyes closed (#2)	**Standing Eyes open (#3)**
Forefoot contacts (F1, F2, F3)	Full foot: 0.51 (-13.5%, 6.8%)	Full foot: <0.001 (-30.8%, -9.6%)
Rearfoot contacts (R1, R2, R3)	Full foot: 0.031 (0.4%, 8.5%)	Full foot: 0.58 (-3.1%, 5.4%)

Table 8: Statistical results for supplemental standing conditions.

The p-values and 95% confidence intervals of all t-tests performed on standing conditions are listed below. Blue text indicates significant perceptual changes ($p \leq 0.05$). Two-tailed t-tests were performed on the full plantar surface of the foot only, not individual ROIs. The lower and upper boundaries of the confidence intervals are in parentheses.

	Standing Prosthesis off (#S1)	**Standing Prosthesis unloaded (#S2)**
Forefoot contacts (F1, F2)	Full foot: 0.23 (-3.0%, 11.8%)	Full foot: 0.021 (-29.2%, -2.5%)
Rearfoot contacts (R2, R3)	Full foot: 0.013 (-11.9%, -1.5%)	Full foot: 0.004 (-9.3%, -1.9%)

Table 9: Statistical results for congruent inputs.

The p-values and 95% confidence intervals of all planned comparisons performed using data from congruent input conditions. Blue text indicates significant perceptual changes ($p \leq 0.05$). One-tailed t-tests were performed on the primary ROI to determine if there was a significant increase in percept size and/or reporting frequency. One-tailed t-tests were also performed on a combination of the two remaining ROIs (regions outside of the primary ROI) to determine if there was a significant decrease in percept size and/or reporting frequency. The confidence intervals are given in parentheses. Because all t-tests were one-tailed, each interval contains positive or negative infinity (abbreviated as 'inf').

	Congruent visual inputs	**Congruent postural manipulations (without vision)**	**Congruent postural manipulations (with vision)**
Forefoot contacts (F1, F2, F3)	Increase in primary ROI: 0.003 (5.9%, Inf) Decrease outside of primary ROI: 0.18 (-Inf, 2.4%)	Increase in primary ROI: 0.004 (6.5%, Inf) Decrease outside of primary ROI: 0.003 (-Inf, -3.6%)	Increase in primary ROI: 0.006 (5.8%, Inf) Decrease outside of primary ROI: 0.005 (-Inf, -2.9%)
Rearfoot contacts (R1, R2, R3)	Increase in primary ROI: 0.066 (-0.6%, Inf) Decrease outside of primary ROI: 0.73 (-Inf, 5.8%)	Increase in primary ROI: 0.046 (0.2%, Inf) Decrease outside of primary ROI: 0.013 (-Inf, -1.5%)	Increase in primary ROI: 0.035 (1.1%, Inf) Decrease outside of primary ROI: 0.49 (-Inf, 4.0%)

Table 10: Statistical results for incongruent inputs.

The p-values and 95% confidence intervals of all planned comparisons performed using data from incongruent input conditions. Blue text indicates significant perceptual changes ($p \leq 0.05$). One-tailed t-tests were performed on the primary ROI to determine if there was a significant decrease in percept size and/or reporting frequency. One-tailed t-tests were also performed on a combination of the two remaining ROIs (regions outside of the primary ROI) to determine if there was a significant increase in percept size and/or reporting frequency. The confidence intervals are given in parentheses. Because all t-tests were one-tailed, each interval contains positive or negative infinity (abbreviated as 'inf').

	Incongruent visual inputs	**Incongruent postural manipulations (without vision)**	**Incongruent postural manipulations (with vision)**
Forefoot contacts (F1, F2, F3)	Decrease in primary ROI: 0.95 (-Inf, 20.2%) Increase outside of primary ROI: 0.027 (1.2%, Inf)	Decrease in primary ROI: 0.87 (-Inf, 15.9%) Increase outside of primary ROI: 0.66 (-6.1%, Inf)	Decrease in primary ROI: 0.53 (-Inf, 10.1%) Increase outside of primary ROI: 0.63 (-6.1%, Inf)
Rearfoot contacts (R1, R2, R3)	Decrease in primary ROI: 0.68 (-Inf, 6.9%) Increase outside of primary ROI: 0.41 (-3.6%, Inf)	Decrease in primary ROI: 0.001 (-Inf, -10.7%) Increase outside of primary ROI: 0.99 (-8.9%, Inf)	Decrease in primary ROI: 0.004 (-Inf, -6.2%) Increase outside of primary ROI: 0.94 (-5.1%, Inf)

CHAPTER 5: Electrically-evoked somatosensation in lower-limb amputees improves performance on an ambulatory searching task

Abstract

Locomotion is a sensorimotor process, yet no commercially available prosthesis offers somatosensory feedback, and lower-limb amputees continue to face locomotor challenges as a result. Somatosensory information can be incorporated into a prosthesis by electrically stimulating the residual nerves of amputees to elicit somatosensory percepts referred to the missing limb. Currently, the functional benefits of sensory-enabled lower-limb prostheses are not well understood. Based on prior animal studies, we developed a horizontal ladder walking test for human participants. Able-bodied individuals and below-knee amputees (BKAs) all performed the test while blindfolded. Two of the BKAs also performed the test while using an implanted closed-loop sensory neuroprosthesis that modulated the perceived location and intensity of pressure applied to the forefoot, midfoot, or rearfoot of the prosthetic foot. We found that BKAs and able-bodied individuals took similar amounts of time to cross the ladder. BKAs made significantly more foot placement errors than able-bodied individuals, with the majority of errors made by the prosthetic limb. Able-bodied individuals typically used the forefoot to step on a ladder rung, while BKAs preferred the midfoot for both limbs. The use of a sensory-enabled prosthesis significantly reduced the number of foot placement errors or the completion times, but it did not change locomotor strategy. In addition to characterizing the efficacy of lower-limb sensory neuroprostheses, this study advanced our

understanding of how cutaneous plantar sensation can be used to acquire action-related information that aids amputees during challenging locomotor tasks. This study also provides a foundation upon which to build future investigations into the role of somatosensation in bipedal ambulation in persons with or without limb loss.

Introduction

Over one million individuals in the United States have a lower-limb amputation (Ziegler-Graham et al., 2008). Despite technological advances in prostheses, amputees still face functional challenges in everyday situations. During locomotor tasks, lower-limb amputees adopt compensatory hip and knee strategies that result in a higher metabolic cost, slower gait, and gait asymmetry (Herr & Grabowski, 2012; Hsu et al., 2006; Isakov et al., 2000; Paysant et al., 2006; Powers et al., 1997; Russell Esposito et al., 2014; Sanderson & Martin, 1997; Torburn et al., 1995; Vickers et al., 2008; Robert L. Waters & Mulroy, 1999) (for a complete review, please see Chapter 1, Background Information: Functional challenges for below-knee amputees). In the long-term, asymmetrical gait leads to chronic lower back, hip, and knee pain (Norvell et al., 2005). One reason why current prostheses appear to have limited effectiveness in addressing deficits exhibited by lower-limb amputees may be because locomotion is a sensorimotor task, and the sensory component is often unaddressed or inadequately addressed by current technologies.

Cutaneous plantar sensation is an essential component of locomotion because it provides information regarding interactions of the foot with the environment.

Mechanoreceptors in the skin of the foot sole transduce spatial and temporal information about contact pressures, and thus indirectly the moment applied at the ankle (P. R. Burgess & Perl, 1973; Kennedy & Inglis, 2002). When plantar sensation is temporarily eliminated in both feet of able-bodied people, postural sway increases (Billot et al., 2013; Hong et al., 2007), posture is more crouched during gait (Hohne et al., 2012), and more reactive steps are needed to restore equilibrium following perturbations (Perry et al., 2000). If cutaneous information is eliminated in just one region of both feet, people shift their body weight away from that region during gait (Nurse & Nigg, 2001). When cutaneous plantar sensation is eliminated in just one foot, people adopt a more cautious walking pattern: dorsiflexion is reduced at the beginning of the stance phase of gait, and plantarflexion is decreased during push-off (Eils et al., 2004). When plantar sensation is eliminated in non-amputees, locomotor characteristics resemble those of lower-limb amputees. The similarities suggest that restoring somatosensory information has the potential to decrease the locomotor deficits exhibited by lower-limb amputees.

One technique for adding sensory feedback to a prosthesis is via peripheral nerve stimulation (PNS) (Charkhkar et al., 2018; Clippinger et al., 1982; Petrini et al., 2019). When stimulating electrical current is applied to an amputee's residual nerves, signals travel to the brain and elicit perceptions of somatosensation. In prior work, we demonstrated that PNS could evoke somatosensory percepts referred to the missing foot of below-knee amputees (Charkhkar et al., 2018). Other prior work has shown that the addition of sensory feedback into a prosthesis can improve functional ability (Clark et al., 2014; Dhillon & Horch, 2005; Hebert et al., 2014; Horch et al., 2011; Petrini et al., 2019; Pylatiuk et al., 2006; Stanisa Raspopovic et al., 2014; Rusaw et al., 2012; J. A. Sabolich et al., 2002; Schiefer et al., 2016; Tan et al., 2014), reduce phantom pain (Dietrich et al., 2012; Petrini et al., 2019; Tan et al., 2014), and enhance prosthesis embodiment (the incorporation of a prosthesis into one's body schema) (Arzy et al., 2006; Emily L Graczyk et al., 2018; Marasco et al., 2011; Mulvey et al., 2012; Schiefer et al., 2016). However, few studies have quantified the functional benefits of sensory-enabled lower-limb prostheses during ambulatory tasks (Clites et al., 2018; Petrini et al., 2019).

The functionality of lower-limb sensory neuroprostheses is not well understood in part because it is challenging to isolate and assess the role of plantar sensation. Humans integrate multiple streams of sensory information, such as vision, vestibular inputs, cognitive attention, somatosensory inputs, and proprioception (Lacour et al., 2008; M. Woollacott & Shumway-Cook, 2002) to interpret and respond to the surrounding environment. When any of these senses are perturbed or eliminated, sensory re-weighting occurs so that tasks can still be completed, but it becomes difficult to identify the contributions of individual senses. Unilateral lower-limb amputees are missing afferent information from sensory receptors in lost muscles, tendons, and skin of one leg, but can compensate for minor threats to stability by reweighting their remaining resources (A. C. Geurts et al., 1992). In particular, they rely on their intact limb and visual inputs during locomotor tasks (Barnett et al., 2013; Isakov et al., 1992). To our knowledge, no existing tests evaluate the role of plantar sensation in one foot at a time while minimizing compensation by vision or the sensory information from the other foot.

The horizontal ladder walking test is an ambulatory searching task that has been routinely applied in sensorimotor research in rodents (Metz & Whishaw, 2002), felines (Bouyer, 2003), and non-human primates (Higurashi, Hirasaki, & Kumakura, 2009). The feline model, in particular, has been utilized to study the role of somatosensation during locomotion. After the cutaneous sensory nerves below the ankle were severed, felines placed their paws on the ladder rungs less precisely than before denervation (Bouyer, 2003). A similar experimental construct has not yet been adapted for bipedal locomotion, which led us to rescale and customize the horizontal ladder test for human participants. We also blindfolded individuals to minimize the contribution of vision to balance control. We conducted this test with volunteers with and without limb loss to characterize the effects of a PNS-based sensory neuroprosthesis.

In this study, our first goal was to quantify how able-bodied individuals and lower-limb amputees performed on the horizontal ladder test, since the evaluation had yet to be applied to either population. We hypothesized that able-bodied people would perform better on the task, demonstrated by faster completion times and fewer foot placement errors. We also expected that able-bodied people would use their forefoot to step on ladder rungs in case corrective ankle movements were needed, and that amputees would use their rearfoot because it is directly underneath the pylon and therefore generates the most repeatable sensory input and most easily distinguished socket-limb pressures. Our second goal was to evaluate lower-limb amputees' performance on the test with a standard prosthesis versus a sensory neuroprosthesis. We hypothesized that receiving somatosensory feedback would improve lower-limb amputees' task performance and alter foot placement strategy to more closely resemble those exhibited by able-bodied individuals.

Materials and methods

Research participants

Fourteen able-bodied volunteers (AB01-AB14), eight women and six men, served as a control group. On average, participants were 34±16 years old (mean+standard deviation) and 1.7±0.08 m tall (Table 11). Six volunteers with unilateral below-knee amputations, commonly referred to below-knee amputees, were also enrolled in this study (BKA01-06). All BKAs were male with a mean age of 57±10 years and height of 1.75±0.08 meters (Table 12). Four below-knee amputations were caused by trauma, one was caused by vascular disease, and one was caused by skin cancer. All amputees were regular prosthesis users and wore their personal prostheses for all experiments. Five BKAs wore energy-storage-and-return (ESAR) prostheses and one BKA wore an active prosthesis with the powered ankle turned off. The Louis Stokes Cleveland Veterans Affairs Medical Center Institutional Review Board and Department of the Navy Human Research Protection Program approved all experimental procedures. PNS portions of this study were conducted under an Investigational Device Exemption obtained from the United States Food and Drug Administration. Participants gave their written informed consent prior to participation in the research related activities described below.

Table 11: Demographics of the able-bodied individuals who participated in the horizontal ladder test.

Subject ID	Age (years)	Height (m)	Gender	Dominant leg
AB-01	31	1.73	Female	Right
AB-02	19	1.68	Male	Left
AB-03	20	1.88	Male	Right
AB-04	18	1.75	Female	Right
AB-05	25	1.78	Female	Right
AB-06	44	1.65	Male	Right
AB-07	19	1.65	Female	Right
AB-08	31	1.73	Female	Right
AB-09	26	1.75	Female	Right
AB-10	58	1.52	Female	Right
AB-11	27	1.68	Male	Right
AB-12	39	1.70	Male	Neither
AB-13	52	1.65	Female	Right
AB-14	66	1.73	Male	Right

Table 12: Demographics of the amputees who participated in the horizontal ladder test.

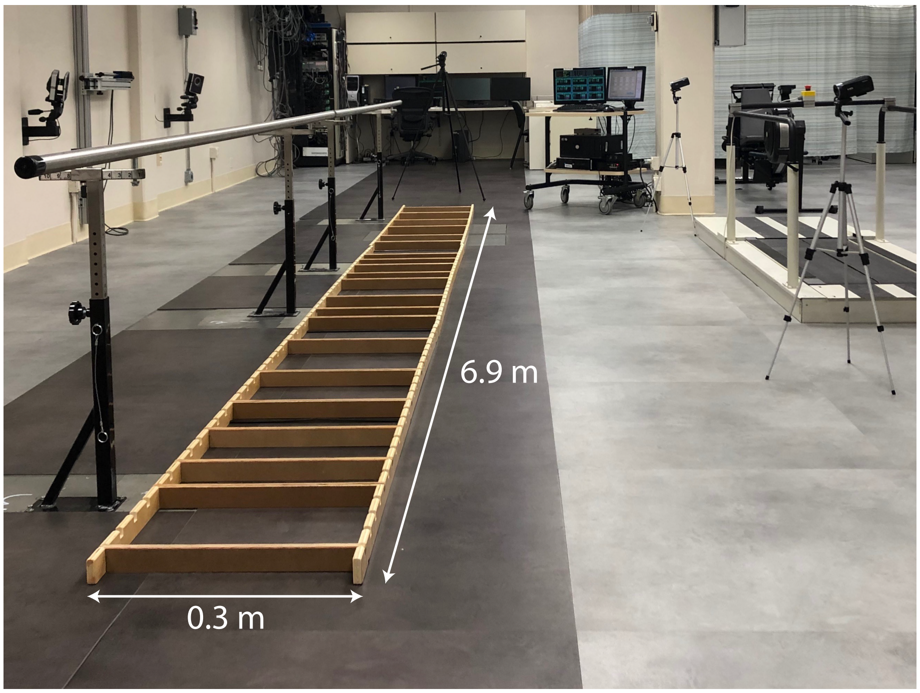
Subject ID	Age (years)	Height (m)	Gender	Amputated Limb	Cause of amputation	Years since amputation	Prosthesis type
BKA01	70	1.73	Male	Left	Trauma	49	ESAR
BKA02	56	1.65	Male	Right	Trauma	11	Active
BKA03	59	1.68	Male	Right	Vascular	5	ESAR
BKA04	58	1.78	Male	Left	Cancer	4	ESAR
BKA05	57	1.83	Male	Right	Trauma	9	ESAR
BKA06	40	1.85	Male	Right	Trauma	2	ESAR

Experimental design

The testing apparatus was constructed out of wood and measured 6.9 m long by 0.3 m wide, as depicted in **Figure 25**. There were 22 ladder rungs in total, each of which was flat on top and 1.9 cm wide. Rungs were randomly spaced 19, 28.5, 38, or 47.5 cm apart. Six different ladder arrangements were used to minimize learning, and participants were blinded to the rung spacing. One trial consisted of crossing the ladder once, taking an optional break, and completing the next trial by crossing the ladder in the opposite

Figure 25: *Horizontal ladder experimental setup.*

Able-bodied participants and participants with amputations performed a horizontal ladder rung walking test while blindfolded. Ladder rungs were randomly spaced 19, 28.5, 38, or 47.5 cm apart and the arrangement changed after every trial. Participants used a parallel bar that ran alongside the ladder for support. Videos were recorded with three cameras, two alongside the ladder and one at the end.



direction. The ladder arrangement changed after a participant had performed it in both directions. Participants used a parallel bar that ran along one side of the ladder to assist with maintaining balance. Two video cameras were set up perpendicular to the ladder along its length for sagittal plane views of the subjects, and a third video camera was placed at the end of the ladder for an orthogonal coronal plane view. Weights were placed around the ladder to ensure that it did not move during an experiment (not pictured in **Figure 25**).

All participants were blindfolded and instructed to: a) walk foot-over-foot, b) step on one rung at a time, and c) not touch the floor or ladder side rails. They were not given instructions about speed. Participants wore their own closed-toe shoes. Force-sensing insoles consisting of eight individual force-sensitive resistor (FSR) cells (iEE, Bissen, Luxembourg) were placed inside each shoe. Pressure readings from each cell were collected with a data acquisition board at a sampling rate of 1000 Hz. The readings were recorded via Vicon Nexus software (version 2.8.2, Oxford, UK) or MATLAB (MathWorks, Inc.; Natick, MA, USA). MATLAB was used only for participants BKA01 and BKA02 because it simultaneously collected pressure data and generated neural stimulation according to the paradigms described later.

Most participants performed two practice trials and 16 data trials. Due to time restrictions, BKA05 performed the task a total of 14 times. To evaluate the effects of the sensory neuroprosthesis, two of the participants with below-knee amputations (BKA01-02) performed additional trials. BKA01 and BKA02 performed the task an additional 12 times without stimulation-evoked somatosensation and 28 times with stimulation-evoked somatosensory feedback.

Outcome measures

We measured number of foot placement errors, completion time, and foot placement strategy. The video cameras were used to identify errors and measure completion time. Errors included: a) missing a rung, b) slipping off a rung, c) simultaneously stepping on a rung and the floor, d) placing the foot on two rungs at once, and e) stepping on a side rail. Foot placement strategy was represented with two measures. First, we used the video recordings to document which foot a participant used to initiate the test. The second measure was to identify which region of the foot was placed on each rung, and required the use of the video recordings and pressure readings. This process was not automated and/or based on pressure readings alone because it was difficult to differentiate between an accidental step on the ground versus a step on a ladder rung. Therefore, each step was verified using video recordings.

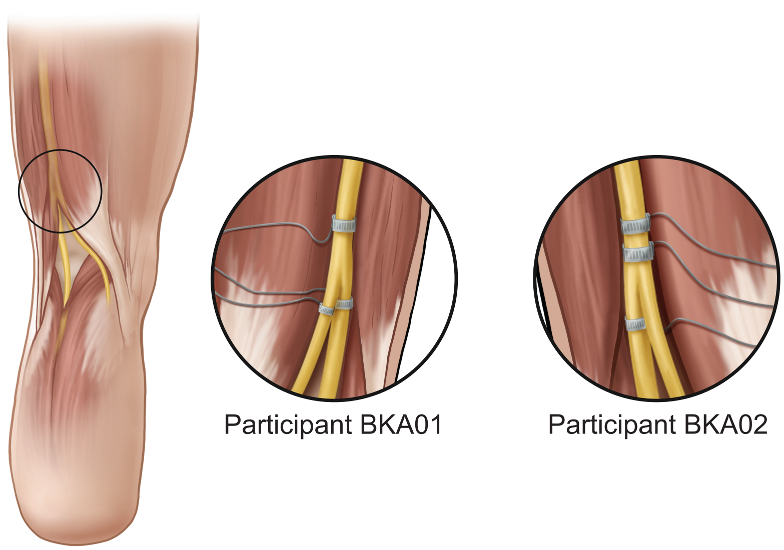
Ground reaction force per step was calculated over a 200 ms window consisting of 100 data samples before and after the time point selected for each step ($\pm$100 ms). This resulted in eight mean pressures, one per FSR cell, for each step on the ladder. We split the FSR cells into three groups corresponding to three regions of the foot. The forefoot region consisted of sensors underneath the first metatarsal, third metatarsal, fifth metatarsal, first phalange, and remaining phalanges. The midfoot sensor was located underneath the middle, lateral side of the foot. The rearfoot region consisted of two sensors placed medially and laterally underneath the heel. The region with the highest average pressure per FSR cell was identified as the region of the foot used to step on the ladder rung.

Closed-loop sensory neuroprosthesis

To deliver neural stimulation, 16-contact Composite Flat Interface Nerve Electrodes (C-FINEs) (Freeberg et al., 2017) were installed around the residual sciatic, tibial and/or common peroneal nerves in Subjects BKA01-02 (**Figure 26**). The internal C-FINEs were connected to an external stimulator (Bhadra et al., 2001; B. Smith et al., 1998) by percutaneous leads that exited the skin on the upper anterior thigh. The details of the implant procedure, post-operative care, and percutaneous access to the contacts within each C-FINE are described in our prior work (Charkhkar et al., 2018). At the time of device implantation, the sensory neuroprosthesis recipients had been without their limbs for 47 years (BKA01) and nine years (BKA02). The experiments in this study were performed at least two years post-implantation, although participants received neural stimulation during weekly laboratory procedures to characterize the psychometric properties of elicited sensations, as well as other experiments to determine the latency, effect of multisensory inputs, and repeatability of the somatosensory responses to stimulation (Charkhkar et al., 2018; Christie, Charkhkar, et al., 2019; Christie, Graczyk, et al., 2019).

Figure 26: *Location of nerve cuff electrodes for participants with below-knee amputations.*

Three 16-contact C-FINEs were implanted around the sciatic, tibial, and common peroneal nerves of subject BKA01 (left) and around the proximal sciatic, distal sciatic, and tibial nerves of subject BKA02 (right). Image courtesy of the APT Center at the Louis Stokes Cleveland VA Medical Center.



Stimulation-induced somatosensation was modulated by pressure applied to the FSRs underneath the forefoot, lateral midfoot, and/or heel regions of the prosthetic foot (**Figure 27**). For each participant, a subgroup of C-FINE contacts was selected such that the stimulating current delivered through them elicited sensation referred to the forefoot, midfoot, or rearfoot of the missing limb (**Figure 28**). The participants had previously reported these regions by drawing the location of the percept on a diagram of an intact foot and leg. The intensity of the electrical stimulus was scaled proportionally to the amount of pressure applied to the FSRs. The perceived magnitude of evoked sensations was modulated by increasing or decreasing stimulation pulse width (Emily L Graczyk et al., 2016). Participants were asked to stand upright without moving as the pressure distribution on the FSRs was captured. Then they were asked to apply pressure to different isolated areas of the foot, such as the forefoot or rearfoot, so that the maximum pressure in each region could be determined. In each position, these pressure ranges were utilized to generate appropriate ranges of stimulation pulse width. Pulse width varied between 120-250 μs. This process was repeated at the beginning of each testing day to ensure confounding factors, such as insole placement within the shoe, were minimized.

__Figure 27:__ Depiction of our closed-loop somatosensory neuroprosthesis.

An insole containing eight FSRs sits underneath the prosthesis, in the shoe. When the amputee puts pressure on the FSRs, it triggers the delivery of electrical stimulation through nerve cuff electrodes to activate sensory fibers in the sciatic nerve. Activation of these sensory fibers causes the amputee to perceive sensations as if they are coming from the missing limb. Image courtesy of the APT Center at the Louis Stokes Cleveland VA Medical Center.

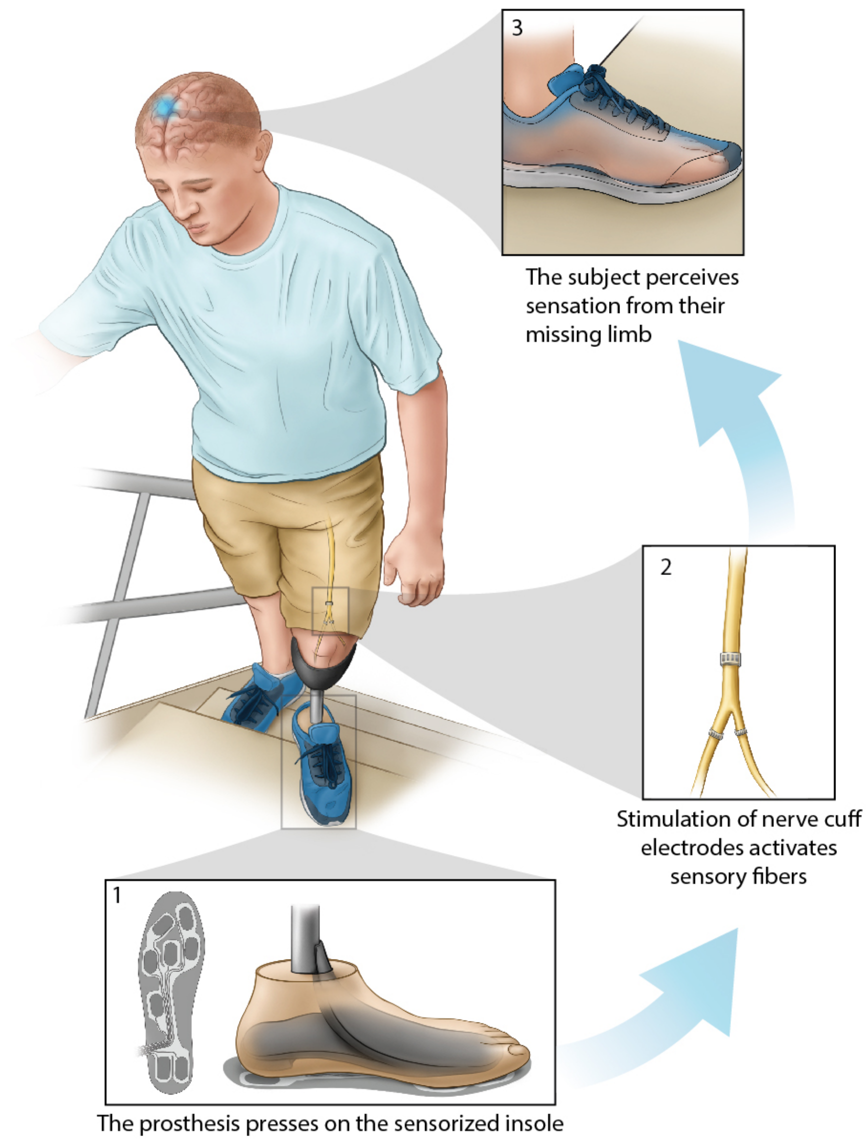
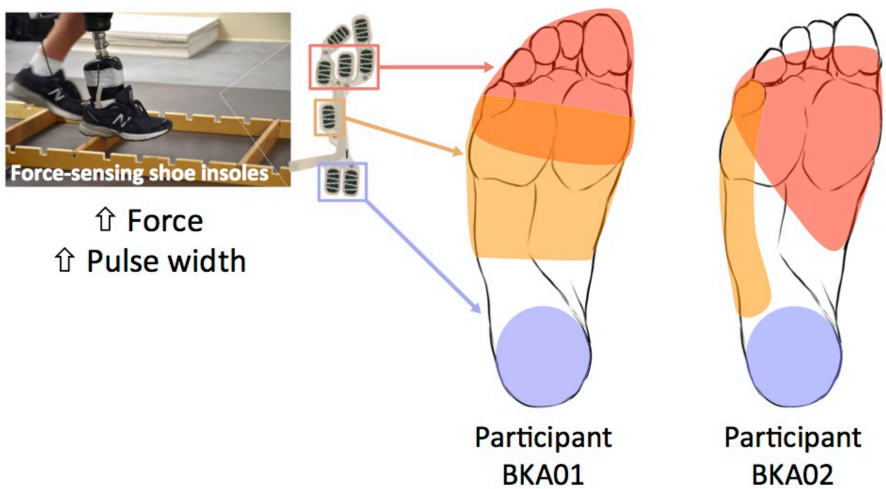


__Figure 28:__ Perceived locations of percepts felt with the closed-loop somatosensory neuroprosthesis.

The insole was split into three regions: the forefoot, midfoot, and rearfoot. Each participant was asked to draw the location of stimulation-induced somatosensory percepts triggered by pressure applied to one FSR region at a time. When pressure was exerted on the forefoot of the prosthesis, the participants reported that percepts occurred in the shaded red area. Percepts reported by pressing on the midfoot and rearfoot are shown in orange and purple, respectively.



Stimulation waveforms were monopolar, asymmetric biphasic, charge-balanced, cathodic-first pulses with return to a common anode placed on the skin above the ipsilateral iliac crest. Pulse amplitude and frequency were set for each C-FINE contact and held constant throughout each session. Pulse frequency ranged from 20 to 100 Hz, and pulse amplitude ranged from 0.7 to 1.2 mA between contacts. Stimulation parameters were set in MATLAB and then sent to a single board computer running xPC Target (MathWorks, Inc.; Natick, MA, USA), which controlled the external stimulator in real time. An isolator between the xPC target computer and the stimulator ensured optical isolation between the participant and line-powered instruments. Stimulation was limited to a charge density of 0.5 μC/mm^2 in order to minimize the risk of tissue and/or electrode damage (Shannon, 1992).

The participants performed a block with up to four trials with or without sensation, took a short break, and then performed another block with or without sensation. This process was repeated with the block order randomized between sensation on or off.

Statistical analysis

To compare the performance of able-bodied individuals versus BKAs, we performed a 16x2 repeated measures linear mixed model (RMLMM). Because BKA03 did not complete all 16 trials, his data were not included in the linear mixed model. The RMLMM approach increased statistical power because the effective sample became 304 data points (19 subjects*16 repetitions) as compared to 19 data points based on the average performance by each individual participant. Repeated measurements on each participant were accounted for by a compound symmetry error covariance structure. With this model, comparisons of the outcome measures were made between groups.

We performed linear regressions to determine if there was an effect of age or height on the outcome measures for able-bodied participants. To determine if there was an effect of gender, we performed a two-tailed, two-sample t-test. We also used three linear regressions to evaluate the relationship between completion time and the number of errors for each group of participants. To compare performance of the BKAs with and without somatosensory feedback elicited by neural stimulation (sometimes referred to as simply "sensory feedback"), each participant served as his own control. One-tailed, two-sample t-tests compared completion time and the number of errors between sensory conditions, with the hypothesis that each outcome measure would decrease during trials with sensory feedback. Significance levels of $\alpha = 0.05$ deemed a statistically significant result.

Results

Foot placement accuracy and trial completion time

Foot placement accuracy was negatively affected by the presence of a lower-limb amputation. Able-bodied individuals made 0.5±0.1 errors per trial (mean±standard error) and BKAs made 1.5±0.4 errors/trial ($p=0.003$, **Figure 29**). For amputees, the majority of the errors were made with the prosthetic foot. Error rate was not affected by age, height, or gender.

Trial completion time was not affected by the presence of a below-knee amputation or demographics. To cross the ladder, able-bodied participants took 48.1±2.4 sec and BKAs took 54.2±5.5 sec (**Figure 30**). We hypothesized that completion time and number of errors were inversely related. Interestingly, there was no significant relationship between these variables for able-bodied individuals (**Figure 31**). For BKAs, however, there was a trend: trials with a higher number of errors were typically completed in a short amount of time ($p<0.001$).

Figure 29: *Foot placement error rates for horizontal ladder test.*

The number of foot placement errors per trial is depicted for able-bodied individuals (AB) and below-knee amputees (BKA). For BKAs, the error rate is stacked to better identify that the majority of the errors were performed by the prosthetic foot (shown in green) rather than the intact foot (in blue). The black bracket indicates that the error rate between the groups was significantly different (p=0.003).

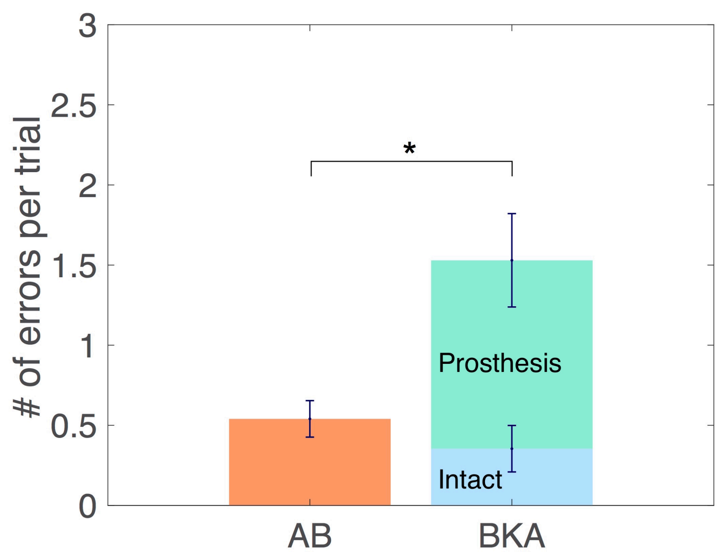


Figure 30: *Trial completion times for horizontal ladder test.*

The trial completion times for able-bodied individuals (AB) are in orange and below-knee amputees (BKA) are depicted in purple. The two groups were not significantly different.

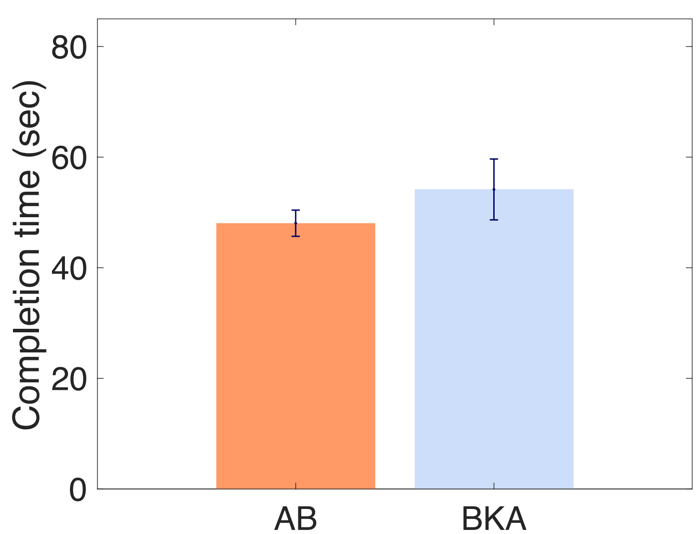
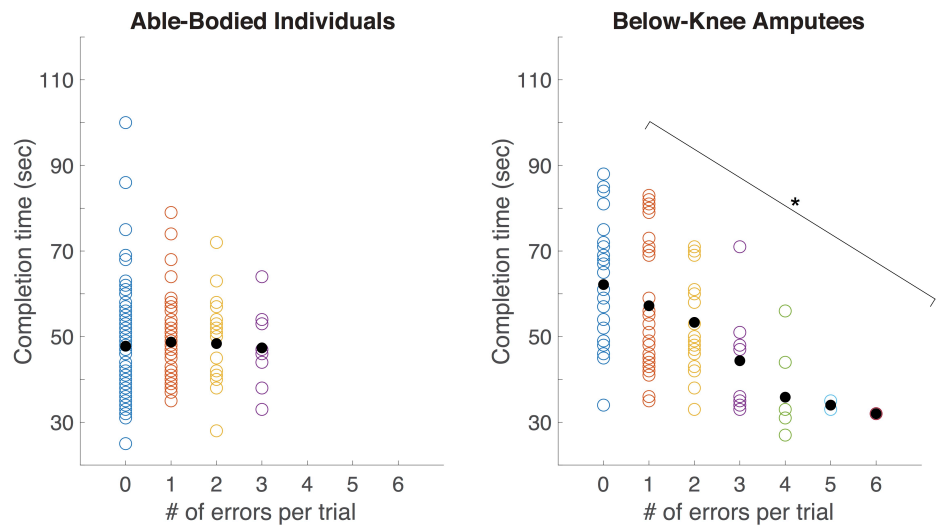


***Figure 31:** Relationship between trial time and foot placement accuracy.*

The bracket indicates that there was a statistically significant relationship (p<0.001) between the number of errors per trial and completion time for below-knee amputees, but not able-bodied individuals.



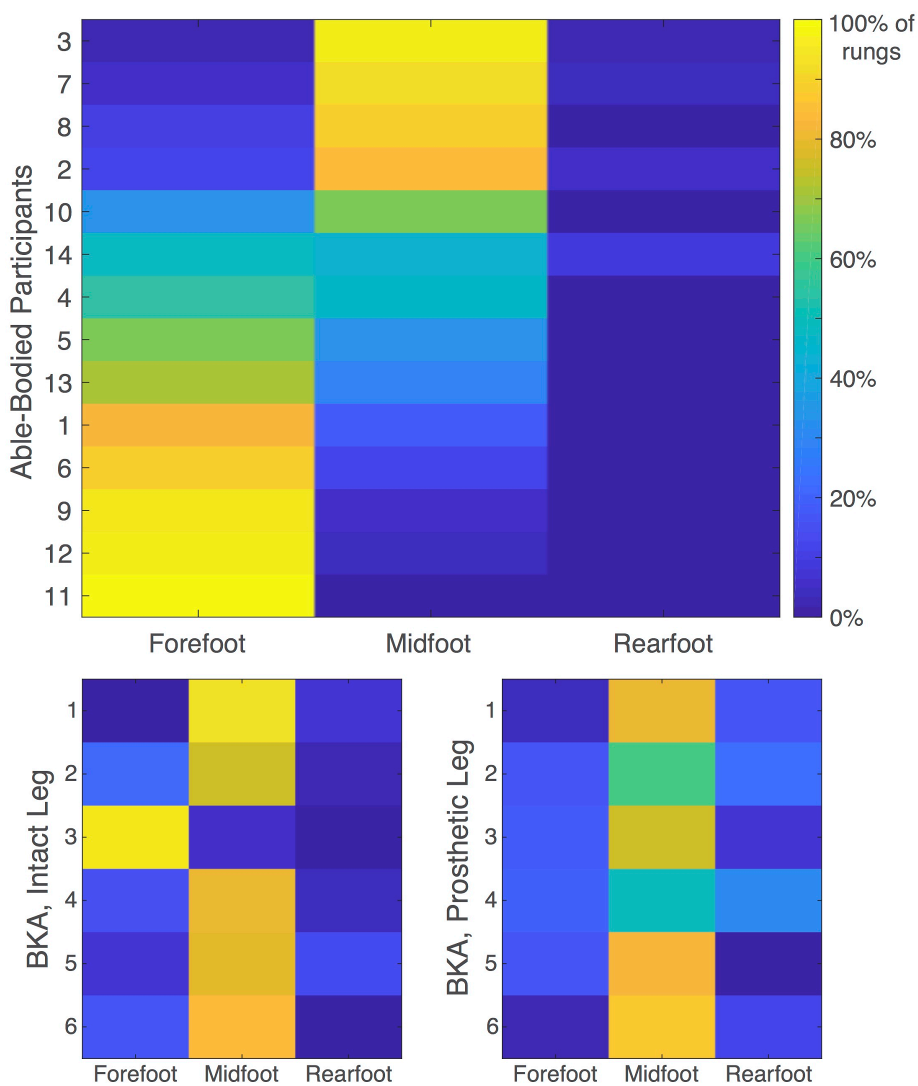
Foot placement strategy

Able-bodied individuals most frequently stepped on a ladder rung with their forefoot (**Figure 32**). Seven volunteers strongly preferred the forefoot (>60% of rungs), five volunteers preferred the midfoot (>60%), and two volunteers split steps almost evenly between the forefoot and midfoot. There was no relationship between error rate and the region of the foot used to step on a ladder rung for either able-bodied individuals or amputees.

With the prosthetic limb, all six BKAs most frequently stepped on the ladder rungs with their midfoot. 13% of total steps with prosthetic limbs were on the forefoot, 72% on the midfoot, and 15% on the rearfoot. Five of these individuals also favored the midfoot with their intact leg. 25% of steps with intact limbs were on the forefoot, 70% on the midfoot, and 5% on the rearfoot.

Figure 32: *Region of the foot used to step on horizontal ladder rungs.*

The 14 able-bodied participants, in the graph on top, were sorted according to how frequently they used the forefoot to step on a ladder rung. Yellow indicates that a foot region was used to step on 100% of the ladder rungs. The results of the six BKAs are broken into two plots in the bottom row: one for the prosthetic leg and one for the affected leg.



Though the first ladder rung was not scored, 10/13 able-bodied participants began at least 75% of trials with their self-reported dominant foot (one able-bodied participant did not have a dominant foot and was excluded from this analysis). 2/13 able-bodied participants began the trial with whichever foot was closest to the supporting handrail. One able-bodied participant chose to use his non-dominant foot in every trial. Five out of the six BKA participants began over 93% of trials with their intact limb. Conversely, participant BKA02 initiated the task with his prosthesis in all but one trial.

BKA task performance with sensory feedback

When two BKAs performed the task with the sensory neuroprosthesis active, the number of foot placement errors per trial significantly decreased for participant BKA02 ($p<0.001$) but not BKA01 (**Figure 33**). Participant BKA01 did not make significantly more errors than able-bodied people, making just 0.3 ± 0.07 errors per trial without somatosensory feedback and 0.4 ± 0.08 errors per trial with feedback from neural stimulation. Participant BKA02 made an average of 2.2 ± 0.4 errors per trial without feedback, and only 1.6 ± 0.3 errors per trial with the neuroprosthesis active. The decrease in error rate with the neuroprosthesis active was predominantly caused by a decrease in errors made with the prosthetic foot ($p=0.02$), not the intact foot.

During trials with sensory neuroprosthesis active, trial time significantly decreased for participant BKA01 ($p=0.01$) but not BKA02 (**Figure 34**). Participant BKA02 performed the test significantly faster than able-bodied individuals ($p<0.001$), taking just 33 ± 0.6 seconds without neural stimulation to cross the ladder and 33 ± 0.5

seconds with the sensory neuroprosthesis active. Participant BKA01 took 68.8±2.0 seconds without stimulation-evoked somatosensory feedback, and 63.3±2.1 seconds with the sensory neuroprosthesis. Even when receiving sensory feedback from the neuroprosthesis, BKA01's trial completion time was still slower than able-bodied individuals ($p<0.001$). Foot placement strategy did not change during trials with the sensory neuroprosthesis active for either the affected or intact limbs (**Figure 35**). Both participants still tended to step on ladder rungs using the midfoot for both limbs, and did not change which foot they initiated the test with.

Figure 33: *Foot placement accuracy for BKA when wearing a sensory-enabled prosthesis.*

Two below-knee amputees, BKA01 and BKA02, also performed the horizontal ladder test using the sensory neuroprosthesis. In the "StimOff" condition, they did not receive stimulation-induced somatosensory feedback. In the "StimOn" condition, they received feedback. The horizontal orange line denotes the mean error rate of the able-bodied participants. The black bracket indicates that the error rate for BKA02 was significantly different between the stimulation conditions ($p<0.001$).

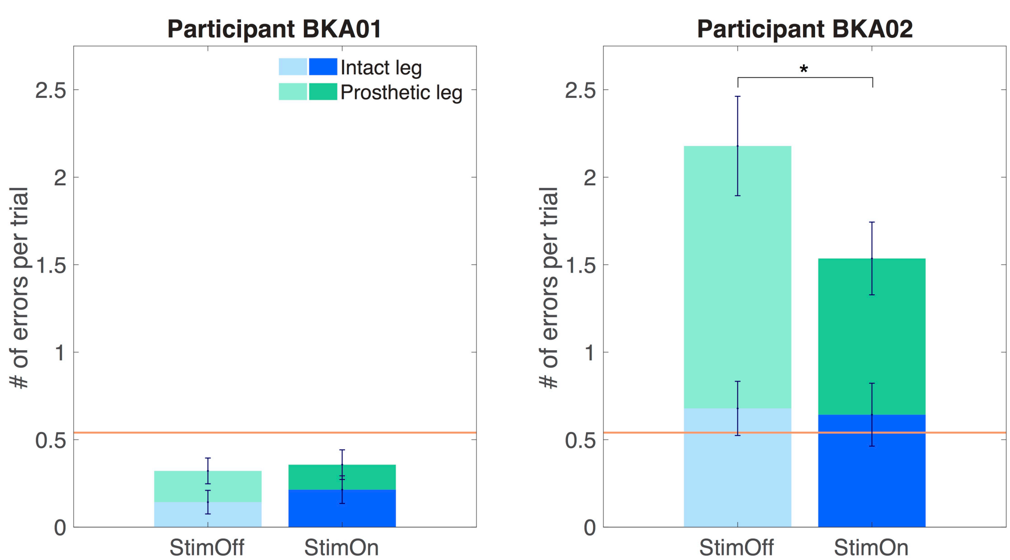


Figure 34: Trial time for BKA when wearing a sensory-enabled prosthesis.

Two below-knee amputees, BKA01 and BKA02, also performed the horizontal ladder test using the sensory neuroprosthesis. In the "StimOff" condition, they did not receive stimulation-induced somatosensory feedback. In the "StimOn" condition, they received feedback. The horizontal orange line demonstrates the mean trial time of the able-bodied participants. The black bracket indicates that the completion time for BKA01 was significantly different between conditions (p=0.01).

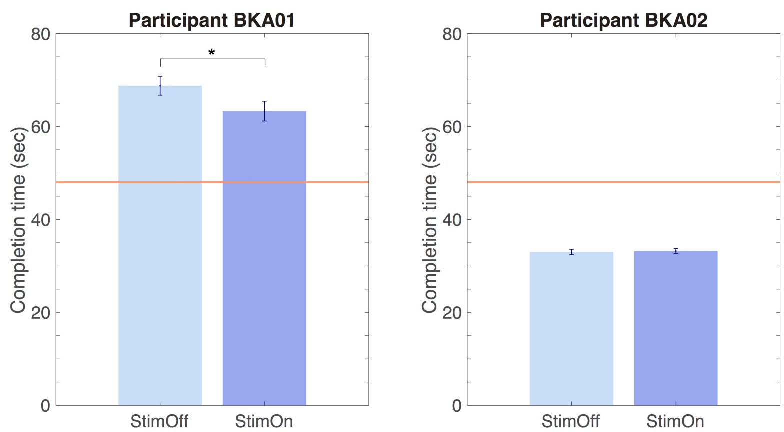
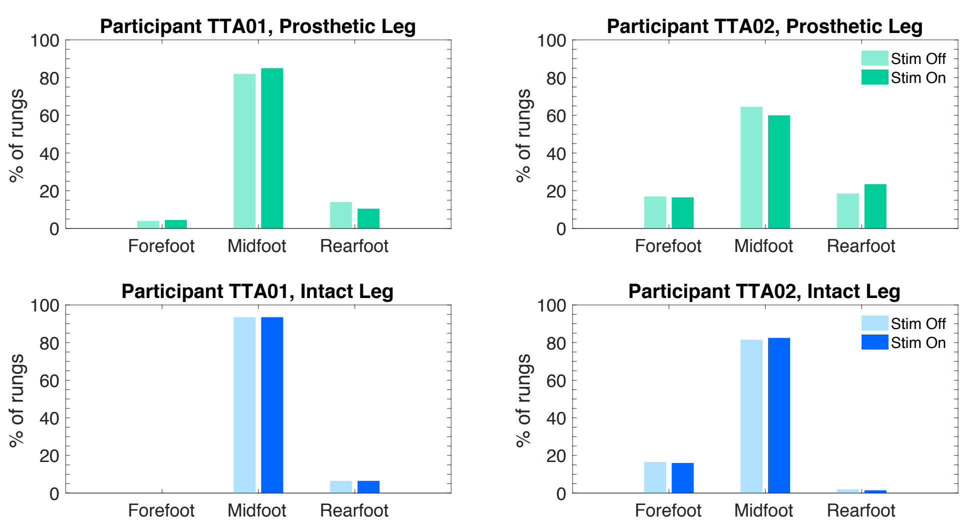


Figure 35: Region of the foot used by BKA to step on ladder rungs when wearing a sensory-enabled prosthesis.

Two below-knee amputees, BKA01 and BKA02, also performed the horizontal ladder test using the sensory neuroprosthesis. In the "Stim Off" condition, they did not receive stimulation-induced somatosensory feedback. In the "Stim On" condition, they received feedback. There were no significant differences in foot placement strategy between the stimulation conditions.



Discussion

Little is known about the role of cutaneous plantar sensation in ambulatory searching tasks. Additionally, few studies have quantified the functional performance of lower-limb sensory neuroprostheses. In this study, we developed a novel ambulatory searching task based on prior animal studies and examined the performance of lower-limb amputees wearing sensory neuroprostheses while performing this task. The differences in foot placement error rate between able-bodied individuals and lower-limb amputees indicate that this task could be suitable for highlighting functional deficits that get masked in existing assessments. Though trial completion time is a commonly used outcome measure (Vereeck, Wuyts, Truijen, & Van De Heyning, 2008), we found that it may not be sensitive enough to detect functional differences in this task. Finally, we found that somatosensory-enabled prostheses can improve the performance of lower-limb amputees in challenging locomotor tasks.

Lower-limb amputees made more errors per trial than able-bodied individuals. The most common mistake amputees made was missing a rung. We hypothesize that this was due to a lack of plantar sensation, which compromised searching strategy, rather than volitional ankle control, which is involved in stabilizing movements (F. B. Horak & Nashner, 1986; Maki & McIlroy, 1997). Even the error rate of the intact foot in amputees was larger than the single-foot error rate in able-bodied individuals, indicating that unilateral amputation affects the searching performance of both legs. We expect this is because amputees have trouble maintaining balance during single-leg stance on the prosthesis and have a lower balance confidence (W C Miller & Deathe, 2004; William C

Miller, Speechley, & Deathe, 2002), which could have caused them to rush. In future studies, it would be interesting for able-bodied participants to perform the task with cutaneous plantar sensation temporarily disrupted in one foot to evaluate this hypothesis.

Moreover, there was an inverse relationship between trial completion time and the number of errors made per trial for BKAs only. Although all participants focused their attention on completing the task, the able-bodied individuals had more compensatory somatosensory and proprioceptive resources to maintain accuracy even at faster speeds. Below-knee amputees were missing tactile and proprioceptive resources from the missing limb, and therefore had to slow down to maintain accuracy. Additional research could be conducted to fully map the relationship between completion time and error rate for able-bodied individuals by instructing them to adopt specific speeds. Overall, our findings could be more generalizable if they are repeated in a larger group of people with more diverse demographics in age, sex, and amputation etiologies.

To step on a ladder rung, able-bodied individuals typically preferred to use the forefoot. The ability to control ankle motion likely impacted how able-bodied individuals placed their feet on ladder rungs. The forefoot has a longer moment arm than the rearfoot with respect to the ankle joint. As a result, ankle moment is highest when load is applied to the forefoot (Erdemir & Piazza, 2002). If an able-bodied individual stepped onto a rung with the forefoot but felt that their position was unstable, they could generate corrective ankle forces to make sure the foot did not slip or touch the ground. In future studies, foot placement strategy could be further evaluated by asking able-bodied participants to perform the task while wearing an ankle-foot orthosis that prevents volitional ankle control.

Conversely, amputees preferred to use the midfoot to step on ladder rungs. One of the amputees explained that he chose this strategy because it was the "safest" location, i.e. the furthest from either end of the foot. Interestingly, five out of the six BKAs preferred to use their midfoot with the intact limb as well, which provides valuable insight into the principles of bilateral foot positioning. The BKAs adopted a strategy that maximized accuracy with the prosthetic leg and mimicked it with the intact leg, despite having a fully functional ankle. Though amputees typically have asymmetric gait patterns (Isakov et al., 2000), bilateral coupling has been seen in prior studies. When navigating stairs, unilateral lower-limb amputees use the same placement strategy for each foot (Ramstrand & Nilsson, 2009). When encountering a sudden obstacle, unilateral lower-limb amputees have temporal delays in muscle activation in both the intact and affected limbs (Hofstad et al., 2009). It has been hypothesized that after amputation, the peripheral nerves undergo a "recalibration" to improve the bilateral comparison of stimuli, which improves locomotor coordination (Kavounoudias, Tremblay, Gravel, Iancu, & Forget, 2005). To gather more insight into this recalibration, the horizontal ladder test should be repeated with more recent amputees and with amputees who do not report gait automaticity, meaning that they have to think about every step they take (Gauthier-Gagnon et al., 1999).

When two BKAs performed the horizontal ladder walking test with sensory-enabled prostheses, performance metrics improved but their locomotor strategies did not change. While performing the ladder test, with or without sensory feedback, BKA01 prioritized accuracy and BKA02 prioritized speed. Sensory feedback from the neuroprosthesis improved whichever aspect was given the lower priority. For BKA01, error rate stayed the same and completion time decreased. For BKA02, completion time stayed the same and his error rate improved. These results were promising and indicate PNS is a suitable technique for delivering sensory feedback. Though PNS does not activate afferent sensory fibers in the same manner as physically-applied tactile stimuli, the body is able to integrate and utilize the evoked somatosensory inputs appropriately in challenging locomotor tasks.

During trials with sensory feedback from the neuroprosthesis, the region of the foot used by BKAs to step on a ladder rung did not change. This was not a negative result, given that the results from able-bodied participants showed no correlation between error rate and foot placement strategy. However, it does highlight that long-term rehabilitative effects, such as a more symmetrical body weight distribution between the legs, might require a longer familiarization period with sensory-enabled prostheses or even a prescribed training regime. To maximize rehabilitative and functional benefits, it might be best for amputees to wear the sensory-enabled prostheses outside of the laboratory for at least several days prior to testing. This added time in different environmental contexts could facilitate gait retraining and the integration of information provided by the sensory neuroprosthesis with other sensory resources. If amputees perform the ladder test after such a training regime and foot placement strategy changes, it will provide more insight regarding how cutaneous plantar sensation is used to acquire action-relevant information, and how that information can eventually modulate locomotor strategies.

The blindfolded, horizontal ladder walking test approximates challenging real-world scenarios in a controlled setting. Normally, unilateral lower-limb amputees can compensate for minor threats to stability using sensory reweighting of their remaining resources (A. C. Geurts et al., 1992). However, in this test, vision is unavailable and the intact limb cannot compensate for the affected limb. The ladder test mimics situations that pose a high fall risk, such as walking outside in the dark or carrying items that block the view of the ground. Clinical measures of balance confidence (Powell & Myers, 1995) could be assessed prior to application of the assessment and utilized as a covariant in future statistical analyses to determine how the fear of falling impacts ambulatory searching. It would also be interesting to conduct the ladder test with fallers and non-fallers to determine if it could be used as a clinical balance tool for those who find current tests too easy, but still have a significant history of falls.

Conclusion

This study probed the role of plantar cutaneous sensation in locomotion using a new ambulatory searching task. We examined how people with lower-limb amputations adapt to the loss of cutaneous plantar sensation, and how that sensation is integrated into the control of bipedal locomotion. The higher error rate in BKAs compared to able-bodied individuals indicated that cutaneous plantar sensation plays a major role in maximizing ambulatory searching strategy. This notion was corroborated in the BKAs who performed the task with sensory neuroprostheses and demonstrated an improvement in performance metrics even without prior practice or training protocols. Our results suggest that the body is able to integrate and utilize PNS-evoked somatosensory inputs appropriately in challenging locomotor tasks. Although sensory neuroprostheses should be tested with a larger population, the findings from this study indicate that sensory neuroprostheses can improve locomotor function in lower-limb amputees.

CHAPTER 6: Conclusions

Summary of aims

The underlying theme of this dissertation is that the temporal synchrony and multisensory integration of PNS-evoked somatosensory feedback assists lower-limb amputees in performing challenging locomotor tasks. Characterizations of temporal synchrony and multisensory integration are important for sensory neuroprosthesis development because current neural stimulation paradigms can only approximate the afferent signals from natural tactile stimuli. Despite these initial differences in fiber activation, the findings in Aim 1 of this dissertation demonstrated that the temporal properties of stimulation-evoked somatosensation and natural somatosensation are not processed and perceived differently. One of our end goals is to integrate the most natural form of sensory feedback with the prosthesis. The naturalness of location, intensity, and temporal properties of sensation evoked by PNS demonstrate that PNS may be suitable for sensory neuroprostheses. In Aim 1, we also established an important design specification for closed-loop sensory neuroprostheses: any hardware or software delays must be below 111 ms in order for stimulation-induced sensation to not be perceived by the amputee as delayed.

In Aim 2, we established that much like natural somatosensation, visual inputs and postural manipulations could reinforce stimulation-induced somatosensory percepts. This interaction had not been previously demonstrated and it is important for sensory neuroprostheses, which will be used in diverse environments with various sensory resources available. This multisensory integration is also useful because force sensor locations within the sensory-enabled prosthesis will rarely align perfectly with the locations of evoked percepts. Fortunately, the addition of visual inputs and postural manipulations can shift stimulation-evoked percepts to more functionally relevant locations, such as the ball and heel of the foot.

The findings from Aims 1 and 2 demonstrated that stimulation-evoked sensation has similar properties to natural somatosensation, however they did not guarantee that the body would utilize the sensory information accordingly. In Aim 3, we showed that evoked plantar somatosensation was indeed utilized by amputees while performing challenging tasks, which reveals an immediate benefit of sensory feedback to lower-limb amputees. The use of a sensory-enabled prosthesis did not change the amputees' locomotor strategy during an ambulatory searching task, which indicated that longer-term therapeutic benefits might require a longer familiarization period with the device, or even a prescribed training regime.

To conclude, the findings from Aims 1 and 2 demonstrated that stimulation-evoked somatosensation is largely perceived as a natural sensory input by the nervous system, and the findings in Aim 3 revealed that amputees could utilize this information in a challenging locomotor task. The hypotheses corresponding to each dissertation aim and brief summaries of the results and implications are also listed below.

Table 13: Aim 1 hypotheses, results, and implications.

Aim 1: Determine if visuotactile temporal synchrony of stimulation-evoked sensation is different than natural somatosensation.		
Hypothesis	*Results*	*Implications*
Natural touch and stimulation-induced sensation are indistinguishable with respect to processing time (PSS) and temporal sensitivity (JND).	The processing time of natural touch and stimulation-induced sensation are not different.	With respect to visuotactile synchrony, stimulation-induced touch is perceived as a natural sensory input. This is a crucial requirement for developing an intuitive sensory-enabled prosthesis that requires minimal training.
	The temporal sensitivity of natural touch and stimulation-induced sensation are not different.	
Processing time, but not temporal sensitivity, is different between trans-radial and below-knee amputees.	Processing time is different between trans-radial and below-knee amputees, following the properties of natural somatosensation.	
	Temporal sensitivity is not different between trans-radial and below-knee amputees, following the properties of natural somatosensation.	
Processing time, but not temporal sensitivity, is influenced by the perceived intensity of stimulation-induced somatosensation.	Processing time is influenced by the perceived intensity of stimulation-induced somatosensation, following the properties of natural somatosensation. As stimulus intensity increased, processing time decreased.	
	Temporal sensitivity is influenced by the perceived intensity of stimulation-induced somatosensation.	Previous studies with natural touch have not identified a definitive impact of stimulus intensity on JND. Our results add to the growing body of literature studying this phenomenon.
Temporal synchrony of stimulation-induced somatosensation does not change over time.	The processing time of stimulation-induced somatosensation does not change over time.	The processing time of PNS-evoked touch appears to rely primarily on transmission dynamics, rather than stimulus modality or familiarity. However, the temporal
	The temporal sensitivity of stimulation-induced	

	somatosensation can change over time.	sensitivity of stimulation-induced touch improves with increased exposure. While training may not be required to operate a sensory neuroprosthesis, it could still be functionally beneficial.
Amputees can perceive when stimulation is delayed by more than 200 ms.	Amputees can perceive when stimulation is delayed by 111$\pm$62 ms.	Hardware and software delays must not allow stimulation to be delayed by more than 111 ms. When temporal discrepancies are consciously detected, it compromises the integration of a prosthesis into the body schema of a user (Shimada et al., 2009).

Table 14: Aim 2 hypotheses, results, and implications.

Aim 2: Assess how visual inputs and postural manipulations affect the size and location of stimulation-evoked somatosensory percepts.		
Hypothesis	*Results*	*Implications*
Changing body position from seated to standing does not impact percept size or location.	Static standing affected percept location with respect to sitting. Percepts covered a smaller percentage of the foot surface for rearfoot electrode contacts, and a larger percentage for forefoot electrode contacts.	The transition from sitting to standing made percepts less discernable due to a lack of informative context cues. This is acceptable, though: when an amputee uses a sensory neuroprosthesis, this condition will not exist. When standing flat-footed, one or more contacts will deliver stimulation to the entire plantar surface of the foot rather than in one distinct region.
	Sensory detection thresholds were not significantly different between sitting and standing.	
	While standing without wearing the prosthesis, there were few differences in percept size compared to a seated position.	
	Donning the prosthesis but keeping it unloaded while standing increased percept size.	
Congruent visual inputs and postural manipulations focus percepts around the location of the input.	Percepts could be focused by congruent visual inputs and/or congruent postural manipulations.	These results could relax certain constraints in the implementation of somatosensory feedback in prostheses. Malleable percepts in functionally relevant locations can improve the fidelity and perhaps the ultimate utility of sensory neuroprostheses in locomotion.
Incongruent visual inputs and postural manipulations draw percepts away from the original location and towards the location of the input.	Visual capture occurred when visual information was incongruent with stimulation-induced sensation.	Our findings are consistent with prior reports on visual capture with natural somatosensation. This demonstrates that stimulation-induced touch is largely perceived as a natural sensory input by the nervous system.
	When postural manipulations and vision	Internal model predictions based on postural manipulations

	were incongruent with somatosensation, the size and/or location of stimulation-induced percepts did not change.	reinforce perceived sensations, but do not alter them. This does not have a direct impact on sensory neuroprostheses, but it does demonstrate how PNS can be used as a neuroscientific tool to study multisensory integration.
	When postural manipulations alone were incongruent with somatosensation, the size and/or location of stimulation-induced percepts did not change.	

Table 15: Aim 3 hypotheses, results, and implications.

<table>
<tr><th colspan="3">Aim 3: Evaluate how stimulation-evoked plantar sensation affects performance in a challenging locomotor test.</th></tr>
<tr><td>Hypothesis</td><td>Results</td><td>Implications</td></tr>
<tr><td rowspan="2">Able-bodied individuals perform this test more quickly and with fewer foot placement errors than amputees.</td><td>Able-bodied people and BKAs did not have significantly different trial completion times.</td><td>Trial completion time may not be sensitive enough to detect functional differences between groups in this task, although it is a commonly used outcome measure in many clinical assessments (Vereeck et al., 2008).</td></tr>
<tr><td>Below-knee amputees made significantly more errors than able-bodied people.</td><td>Cutaneous plantar sensation is necessary for maximizing ambulatory searching strategy.</td></tr>
<tr><td rowspan="2">Able-bodied individuals primarily use the forefoot to step on a ladder rung, whereas amputees primarily utilize the forefoot for the intact leg and the rearfoot for the affected leg.</td><td>Able-bodied individuals primarily used the forefoot to step on a ladder rung. There was no correlation between foot placement strategy and error rate.</td><td>The ability to control ankle motion likely impacted how people placed their feet on ladder rungs, but it was not correlated with accuracy. This indicates that the horizontal ladder test may be a sufficient tool for advancing our understanding of how people adapt to the loss of cutaneous plantar sensation, and how that sensation is integrated into the control of bipedal locomotion.</td></tr>
<tr><td>For both the intact leg and affected leg, BKAs used the midfoot to step on a ladder rung. One of the amputees explained that he chose to step on the rungs with his midfoot because it was the “safest” distance, i.e. the furthest from either end of the foot.</td><td>These results support the hypothesis that after amputation, the peripheral nerves undergo a “recalibration” to improve the bilateral comparison of stimuli, which improves locomotor coordination.</td></tr>
</table>

During trials in which BKAs use the sensory neuroprosthesis, foot placement accuracy increases and trial time decreases.	With or without sensory feedback, BKA01 prioritized accuracy and BKA02 prioritized speed. Sensory feedback improved whichever aspect was given the lower priority. For BKA01, error rate stayed the same and completion time decreased. For BKA02, completion time stayed the same and his error rate improved.	Even without prior training, BKAs utilized stimulation-evoked plantar sensation while performing challenging tasks. This reveals an immediate benefit of sensory neuroprostheses to lower-limb amputees.
During trials in which BKAs use the sensory neuroprosthesis, amputees primarily use the forefoot or midfoot to step on ladder rungs.	Foot placement strategy did not change during trials with sensory feedback.	Long-term rehabilitative effects, such as more symmetrical body weight distribution between the legs, might require a longer familiarization period with the sensory-enabled prosthesis, or even a prescribed training regime.

Innovation and significance

Using peripheral nerve stimulation, we were able to decouple sensory stimuli in a way that is not ordinarily possible, thus providing an unprecedented opportunity to probe the underlying characteristics of human multisensory integration. In Aim 1, this decoupling enabled the evaluation of subjective simultaneity in a functional context. We demonstrated that temporal synchrony could be verified without instrumenting a closed-loop sensory neuroprosthesis, which will save time and resources in future studies. Secondly, decoupling stimuli gives insight into how the brain processes multisensory delays. The results of the functional delay task in Aim 1 provided supporting evidence for a common viewpoint that the brain maintains multisensory synchrony by having a window of temporal integration (Keetels & Vroomen, 2012). Finally, this decoupling protocol allowed us to create incongruent scenarios that provide a unique framework to examine which regions of the brain are involved in establishing congruency between two inputs.

The work in Aim 1 was one of the first to compare the temporal perceptual properties of stimulation-induced sensation to natural tactile sensation. It was also one of the first to compare upper- and lower-limb amputees with respect to somatosensation evoked in missing limbs. Our findings provide important input requirements for prosthesis design and define characteristics of artificial stimulation needed to mimic the naturalistic perception. Prior to the study in Aim 2, the effect of posture manipulations on tactile localization had received little attention with respect to locomotion, even in able-bodied individuals. We found that percepts evoked by cuff electrodes could be shifted to more functionally relevant locations by redundant multisensory inputs. This suggests that the selectivity of cuff electrodes is sufficient for functional applications, which has significant implications for the field of sensory neuroprostheses and neural interfaces. When neural interfaces such as intrafascicular electrodes are implanted, they are closer to the neural fibers of interest. As a result, they can activate smaller populations of fibers at a time, and evoke higher resolution percepts. However, our results suggest that more invasive devices may not be required to obtain sufficient functional performance.

By characterizing temporal synchrony and multisensory integration, we demonstrated that stimulation-evoked somatosensation is largely perceived as a natural sensory input by the nervous system. Though the initial activation of fibers is different than physically-applied tactile stimuli, this new sensory resource is integrated into the biological system and processed appropriately. In Aim 3, we showed that the nervous system can utilize this PNS-evoked plantar sensation to aid amputees' performance during challenging tasks. The studies conducted in Aim 3 and Appendix A were some of the first to functionally evaluate below-knee prostheses equipped with PNS-induced somatosensory feedback. Prior studies involving vibratory and electrocutaneous sensory feedback had marginal functional improvements during gait and static and dynamic standing (Rusaw et al., 2012; J. A. . Sabolich & Ortega, 1994), and intraneural and extraneural stimulation had only been tested with above-knee amputees (Clippinger et al., 1982; Petrini et al., 2019). The work in Aim 3 and Appendix A demonstrated that for unilateral below-knee amputees, sensory neuroprostheses are the most beneficial in environments that compromise other compensatory balance resources.

Finally, in many traditional balance tests, the effects of PNS-evoked somatosensation may be masked because amputees are able to maintain balance using their remaining sensory resources. This makes it difficult to assess the functionality and utility of lower-limb sensory neuroprostheses. To our knowledge, no tests existed that evaluated the role of human plantar sensation in one foot at a time while minimizing compensation by other sensory resources. Based on the compelling evidence from animal studies on the suitability of the horizontal ladder test for examining the role of somatosensation during locomotion, we rescaled and customized the horizontal ladder test for humans. This task provides a foundation upon which to build future studies of investigations into the role of somatosensation in bipedal ambulation in persons with or without limb loss.

Future work

Additional target populations

The knowledge gained in this dissertation lays the groundwork for future studies with different populations and anatomical targets. We primarily focused on restoring sensation to unilateral below-knee amputees, but some issues may also be relevant to above-knee amputees and/or bilateral lower-limb amputees. Both above-knee and bilateral amputees are missing more somatosensory and proprioceptive resources than unilateral below-knee amputees. Both populations have a harder time maintaining balance and performing locomotor tasks than able-bodied individuals and unilateral below-knee amputees (Akarsu, Tekin, Safaz, Göktepe, & Yazicioğlu, 2013; Helm, Engel, Holm, Kristiansen, & Rosendahl, 1986; William C. Miller, Deathe, Speechley, & Koval, 2001; Nolan et al., 2003; R. L. Waters, Perry, Antonelli, & Hislop, 1976), and could benefit substantially from adding balance resources, such as somatosensation, back into their postural reserve.

The electrodes in this study were implanted near the popliteal fossa, but could be implanted more proximally. In a previous study, we observed a high overlap in reported percept locations between distal versus proximal nerve cuff electrodes, suggesting that the same sensory responses could be elicited from more proximal points on the nerve (Charkhkar et al., 2018). This would benefit people with more proximal amputations and people who lost a limb due to dysvascular neuropathy, and have nerve damage distally but intact nerves proximally. This is a huge population: 81% of major lower-limb amputations are caused by vascular disease, such as diabetic peripheral neuropathy, and that number is growing rapidly each year (Ziegler-Graham et al., 2008). For individuals who have been identified by physicians as having a high risk of amputation, it could be beneficial to apply extraneural stimulation to encourage continued and proper use of the lower-extremities and delay/prevent amputation.

In addition, all of the amputees participating in these dissertation studies were at least two years post-amputation. Recent amputees who are still undergoing rehabilitation may benefit from the most from somatosensory feedback, because they are still adjusting to the loss of tactile sensation and proprioception from the amputated limb. Sensory feedback referred to the missing limb may give them more trust in their new prostheses, possibly preventing overuse of the intact limb and the resulting consequences, such as osteoarthritis of the intact knee and/or hip (Gailey et al., 2008).

PNS versus sensory substitution

In this dissertation, we established that PNS-evoked somatosensation is perceived as a natural sensory input by the nervous system, and amputees can utilize this information in challenging locomotor tasks. To our knowledge, sensory substitutive feedback has not been evaluated according to procedures in Aims 2 and 3. It is possible that substitutive sensory stimuli may be processed naturally by the nervous system, but they do not integrate with the other senses and are therefore not interpreted for use in a challenging task. This could help to explain why there are few commercially available devices with sensory substitutive feedback. I propose asking the same group of individuals to perform Aims 2 and 3 using different sources of sensory feedback, such as vibration and transcutaneous electrical stimulation. The results may explain why sensory substitution devices are not widely used, and it would be useful in justifying if extraneural and intraneural interfaces are worth the risks and burden of surgery.

Integrating sensory neuroprostheses with volitional ankle control

To our knowledge, no studies have characterized the performance of a lower-limb prosthesis equipped with a volitionally-controlled ankle and plantar sensory feedback. As previously mentioned, myoelectrically-controlled prosthetic ankles have marginal improvements on the kinematics and kinetics of locomotion (Kannape & Herr, 2016). In Aim 3 and Appendix A, we demonstrated that sensory-enabled below-knee prostheses are most beneficial in environments that compromise remaining balance resources. The combination of motor control with sensory feedback may maximize the functionality of lower-limb prostheses.

Able-bodied locomotion is controlled by a central pattern generator (CPG), which is a neuronal network within the central nervous system that generates a rhythmic pattern of motor activity (Kandel et al., 2000). Though CPGs are not controlled via phasic sensory input from peripheral receptors, tactile information from mechanoreceptors and proprioceptive information from golgi tendon organs and muscle spindles are continuously integrated with a CPG (Kandel et al., 2000)(Frigon & Rossignol, 2006). The basic pattern produced by a CPG can also be modified by visual and vestibular information (Kandel et al., 2000). These modifications enable us to generate appropriate motor commands in response to external demands. Therefore, combining volitional prosthetic ankle control with plantar sensory feedback could be crucial for developing prostheses that more closely resemble intact limbs.

Take-home system

In Aim 3, we found that long-term therapeutic benefits might require a longer familiarization period with a sensory neuroprosthesis, or even a prescribed training regime. In future studies, study participants should wear sensory-enabled prostheses for longer periods of time at home and in community settings. This additional time in different environmental contexts may facilitate gait retraining. To analyze the effects of this prolonged familiarization period, the participants could repeat the horizontal ladder test after wearing the device outside of the laboratory. If foot placement strategy changes, it would suggest that cutaneous plantar sensation is used to acquire action-relevant information and then modulates locomotor strategies.

Appendix A: Sensory neuroprosthesis improves postural stability under challenging balance conditions in lower-limb amputees

The following is a copy of the paper "Sensory neuroprosthesis improves postural stability under challenging balance conditions in lower-limb amputees" submitted to the journal *Scientific Reports* on 31 October 2019.

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Abstract

To maintain postural stability, unilateral lower-limb amputees (LLAs) heavily rely on visual and vestibular inputs, and somatosensory cues from their intact leg to compensate for missing somatosensory information from the amputated limb. When any of these resources are compromised, LLAs exhibit poor balance control compared to able-bodied individuals. We hypothesized that restoring somatosensation related to the missing limb via direct activation of the sensory nerves in the residuum would improve the standing stability of LLAs. We developed a closed-loop sensory neuroprosthesis utilizing non-penetrating multi-contact cuff electrodes implanted around the residual nerves to elicit perceptions of the location and intensity of plantar pressures under the prosthetic feet of two transtibial amputees. Effects of the sensory neuroprosthesis on balance were quantified with the Sensory Organization Test and other posturographic measures of sway. In both participants, the sensory neuroprosthesis improved equilibrium and sway when somatosensation from the intact leg and vestibular inputs were perturbed simultaneously. One participant also showed improvement with the sensory neuroprosthesis whenever somatosensation in the intact leg was compromised. These observations suggest the sensory feedback elicited by neural stimulation can significantly improve the standing stability of LLAs, particularly when other sensory inputs are depleted or otherwise compromised.

Introduction

Individuals with lower limb amputation face challenges in maintaining their balance when navigating uneven terrains or encountering perturbations during walking (Barnett et al., 2013; Lamoth, Ainsworth, Polomski, & Houdijk, 2010; Vanicek et al., 2009). The fear of falling and decreased balance confidence are prevalent among lower limb amputees (LLAs) (William C. Miller, Deathe, et al., 2001; Vanicek et al., 2009), which are important factors in their mobility and participation in social activities (Asano, Rushton, Miller, & Deathe, 2008; Jayakaran, Johnson, Sullivan, & Nitz, 2012; W C Miller & Deathe, 2004; William C. Miller, Deathe, et al., 2001; Nederhand et al., 2012). Compared to individuals without lower limb loss, LLAs have slower walking speeds, possibly because of decreased gait stability and the need for increased conscious attention while walking on uneven or changing terrains (Lamoth et al., 2010). In a survey of community-dwelling LLAs, more than 50% reported that they had fallen at least once in the past year (Kulkarni et al., 1996; William C. Miller, Deathe, et al., 2001). Amputees typically place more trust in the intact limb, which results in overuse and destructive long-term consequences, such as osteoarthritis of the intact knee and/or hip (Gailey et al., 2008). Decreased loading on the affected limb can also lead to osteopenia and subsequent osteoporosis. With the growing number of people who lose limbs due to vascular diseases or trauma, it is important to develop assistive technologies that improve standing stability in this population.

Three main sensory systems, the visual, vestibular, and somatosensory, contribute to stable posture during stance (Chien, Eikema, Mukherjee, & Stergiou, 2014; Chien, Mukherjee, Siu, & Stergiou, 2016). Theses inputs are integrated and processed in the central nervous system which generates appropriate movement strategies and motor commands to maintain postural stability (Day, 2002; Pedalini, Cruz, Bittar, Lorenzi, & Grasel, 2009). However, when any of the sensory inputs are absent or inaccurate, the CNS adjusts the gains for each input to control the stability (Day, 2002). Such adjustments are often demonstrated in increased body sway, and if not successful can result in loss of balance and falls.

The absent sensory feedback from the missing foot in LLAs plays a crucial role in the degradation of their balance (Isakov et al., 1992; Quai, Brauer, & Nitz, 2005; Van Deursen & Simoneau, 1999). LLAs mainly rely on other sensory inputs, such as vision or proprioception from the intact and residual lower limbs, to compensate for compromised sensory information (Barnett et al., 2013; Isakov et al., 1992). When vision is blocked, LLAs have significantly more postural sway and are less stable compared to able-bodied controls (Duclos et al., 2009; Nadollek, Brauer, & Isles, 2002), indicating that the lack of somatosensory feedback from the missing limb contributes to the marked differences in stability (Isakov et al., 1992). Moreover, unilateral amputees use sensory feedback from their intact ankle and foot to compensate for the somatosensory information lost with the missing limb. Studies show unilateral amputees rely more on their intact limb to make balance adjustments and reduce the risk of fall (Claret et al., 2019). When LLAs have trouble maintaining balance with their intact leg, they are more likely to have poor functional outcomes related to personal care, household activities, and recreational activities (Schoppen et al., 2003).

Electrical stimulation of the remaining nerves in the residual limb of LLAs via various neural interface technologies can elicit somatosensory percepts referred to the missing limb (Charkhkar et al., 2018; Petrini et al., 2019). The modality and the intensity of the reported sensations can be modulated by tuning the stimulation parameters (Charkhkar et al., 2018). The sensations evoked by non-penetrating multi-contact cuff electrodes implanted on the peripheral nerves above the knee in the residual limbs of LLAs have been robust and consistent for more than two years. Furthermore, the perceived sensations generated by neural stimulation have central processing times and temporal sensitivities similar to natural tactile sensation (Christie, Graczyk, et al., 2019). Although LLAs report improvements in self-reported confidence with the sensory feedback elicited by neural stimulation (Clippinger et al., 1982; Petrini et al., 2019), the effects of such feedback on objective measures of balance has not previously been determined.

The Sensory Organization Test (SOT) has been utilized as a clinical and research tool to objectively and quantitatively examine the contribution of different sensory systems to standing balance (Chien et al., 2016). In the SOT, visual, vestibular, and somatosensory inputs are selectively perturbed (**Figure 36**), and the results on postural control are examined individually and in combination (Jayakaran et al., 2012). Outcomes of the test are correlated to overall balance performance during ambulation and activities of daily living (Judge, King, Whipple, Clive, & Wolf Son, 1995; Vanicek et al., 2009). The SOT has been administered on different patient populations with standing stability deficits, including stroke survivors (Smania, Picelli, Gandolfi, Fiaschi, & Tinazzi, 2008), individuals with Parkinson's Disease (Gera, Freeman, Blackington, Horak, & King, 2016; Nocera, Horvat, & Ray, 2009), LLAs (Barnett et al., 2013; Vanicek et al., 2009), and elderly people (Judge et al., 1995; Pedalini et al., 2009).

Standing balance is one of the most basic tasks in amputee rehabilitation and plays an essential role in most functional activities (Erbahceci, Yigiter, Sener, Bayar, & Ulger, 2001; Van Deursen & Simoneau, 1999). In this study, we examined whether the sensory feedback provided by chronically implanted non-penetrating, epineural nerve cuff electrodes could improve balance stability in transtibial amputees. Our hypotheses were: 1) somatosensory feedback elicited by direct neural stimulation will reduce the sway exhibited by LLAs when other sensory inputs are perturbed, and 2) electrically elicited sensations related to the missing foot will improve weight distribution symmetry between the intact and prosthetic limbs. The results of this study may have implications to the development of new prosthetic technologies intended to reduce the risk and fear of falls, improve standing balance and balance confidence, encourage engagement in unstructured community environments, or accelerate the rehabilitation process following lower limb amputation.

Methods

Research participants

Two individuals with unilateral transtibial amputations (LL01 & LL02) volunteered and enrolled in this study. A summary of their characteristics at the time of enrollment is presented in Table 16. Both participants were regular prosthesis users with no medical history of peripheral neuropathy, dysvascular disease, phantom pain, or uncontrolled diabetes. Participants had no fall history for at least nine months prior to the beginning of the study, and were therefore both classified as non-fallers (Vanicek et al., 2009). The experiments described in this work were conducted at least a year after enrollment. However, during the first year post nerve cuff implantation, both participants regularly visited the laboratory where they received neural stimulation and performed other tests including impedance measurements, sensory threshold determination, sensory mapping, and psychometric experiments described elsewhere (Charkhkar et al., 2018; Christie, Charkhkar, et al., 2019; Christie, Graczyk, et al., 2019). The Louis Stokes Cleveland Veterans Affairs Medical Center Institutional Review Board and Department of the Navy Human Research Protection Program approved all study procedures, which were conducted under an Investigational Device Exemption obtained from the United States Food and Drug Administration. The study was designed in accordance with relevant guidelines and regulations, and both individuals gave their written informed consent to participate.

Neural interface technology

The details of neural interface technology and implantation technique have been described previously (Charkhkar et al., 2018). Both participants had 16-contact Composite Flat Interface Nerve Electrodes (C-FINEs) installed around their sciatic, tibial and/or common peroneal nerves during an outpatient surgical procedure. All C-FINE contacts were connected to percutaneous leads via industry-standard 8-contact in-line connectors (Medtronic Inc.). The percutaneous leads exited the skin on the upper anterior thigh. To deliver stimulating currents during laboratory visits, the percutaneous leads from C-FINEs were connected to a custom-designed external stimulator. **Figure 37** depicts schematically the implanted and external components of the system.

Electrical stimulation

The pulse amplitude range for the external stimulator was 0-5.6 mA with the resolution of 0.1 and 0.2 mA for values below and above 2 mA, respectively. The pulse width could be modulated between 0-255 μs with a resolution of 1 μs. Stimulating currents were delivered to the nerves in a series of asymmetric, charge-balanced, cathodic-first pulses with return to a common anode placed on the skin above the iliac crest. Stimulation parameters were set through a custom-made routine in Simulink (MathWorks Inc.) and then compiled and downloaded into a dedicated computer running xPC Target real-time kernel (MathWorks Inc.) for real-time operation during standing experiments. An optical isolator between the xPC target computer and the stimulator ensured electrical isolation between the participant and other AC-powered electrical equipment. Stimulation charge density was kept below 60 uC/cm^2 to avoid any potential of damage to the neural tissue and/or platinum contacts (Shannon, 1992).

Sensory neuroprosthesis

For each participant, a subgroup of C-FINE contacts was selected such the stimulating currents delivered through them elicited sensation in either the forefoot or the heel. This selection was based on prior mapping experiments (Charkhkar et al., 2018). The pressure distribution under the prosthetic foot was measured using dynamic force sensing resistors (FSRs) incorporated into a shoe insole (IEE S.A.). Each insole contained eight individual FSR cells, and readings from all cells were collected using a data acquisition board with a sampling rate of 1000 Hz. The selected C-FINE contacts delivered the stimulating current to elicit sensations in locations of the missing limb which corresponded to the pressure distribution under the prosthetic foot during standing (**Figure 27**). Stimulation pulse width (PW) varied proportionally in response to pressure readings from FSR insole cells to modulate the intensity of the perceived sensation. To determine nominal pressure values, participants were asked to stand upright while the pressure distribution on the FSRs was captured during stance. Then, they were asked to apply pressure to different areas of the foot including the forefoot and heel so that the maximum regional pressures could be determined. In each position, the voltage readings from FSRs were utilized to determine which C-FINE contact to deliver stimulation and the range of PW values. This process was repeated at the beginning of each testing day to ensure confounding factors, such as insole placement and changes in prosthetic fit, were minimized.

Experimental design

The SOT was administered using a SMART Balance Master (Natus Medical Inc.). The device was equipped with a controllable platform with two embedded dynamic force plates capable of anterior-posterior translation or rotating about the ankle, and a visual surround capable of rotating about the subject. Movements of the platform and visual surroundings were controlled by the NeuroCom Balance Manager Software Suite (Natus Medical Inc.). Participants were tested under six sensory conditions while they were secured in a loosely fitting safety harness attached to an overhead bar. The conditions for the SOT, as listed in Table 17 and illustrated in **Figure 36**, involve visual, vestibular, and/or somatosensory perturbations. Rotations of the platform and/or the visual surroundings in the fore-aft direction was proportionally matched with a gain to the sway of each participant during the test, such that higher postural sway resulted in greater perturbations in the platform or visual surroundings. The gain was selected after test trials in which participants found it difficult to maintain their balance during the most challenging condition (#6 – vestibular and somatosensory inputs compromised), yet not to a degree that it would result in a fall.

Each SOT condition lasted for 20s and participants were instructed to maintain as little postural sway as possible, to keep their feet in the same position throughout the test, and to keep their arms at their sides. One test block consisted of all six SOT conditions, with each condition tested two times. Each block was performed under one sensory stimulation mode: closed-loop sensory neuroprosthesis active (stimulation "on") or inactive (stimulation "off"). The order of conditions was randomized within each block, and the order of stimulation modes was randomized between blocks. Six blocks were collected for each sensory stimulation mode in total, i.e. 12 trials for each SOT condition and sensory stimulation mode.

For every trial, the time series of ground reaction forces, center of pressure (COP), and estimates of Center of Gravity (COG) were extracted using the clinical module in the NeuroCom Balance Manager Software Suite. The raw force plate data were sampled at 100 Hz and saved on a local hard drive for offline processing.

Data analysis and outcome measures

Equilibrium Score (ES), a clinically known measure to quantify sway amplitude during SOT conditions (Barnett et al., 2013), was calculated for every trial based on Equations 5 and 6, consistent with the built-in equations used in NeuroCom Software

Suite clinical module (Alberts et al., 2015; Ji, Findley, Chaudhry, & Bukiet, 2004).

$$ES = 100 \times \frac{12.5^{o} - (Max(\theta_A) - \ Max(\theta_P))}{12.5^{o}}$$

Equation 5

In Eq. 5, $Max(\theta_A)$ and $Max(\theta_P)$ are the maximum COG angular sways in the anterior and posterior directions, respectively. 12.5^{o} is an accepted range of anterior to posterior sway before an able-bodied individual loses balance during stance (Chaudhry, Bukiet, Ji, & Findley, 2011; Chaudhry et al., 2004). An ES approaching 100 denotes minimal sway, whereas scores around zero indicate that balance is approaching the limits of stability. The $Max(\theta_{A\ or\ P})$ was calculated using Equation 6, in which h is the participant's height (Alberts et al., 2015):

$$Max(\theta_{A\ or\ P})(deg) = \ \tan^{-1}\left(\frac{Max\ (COG_{A\ or\ P})(cm)}{0.55{\times}h\ (cm)}\right){\times}\frac{180^{o}}{\pi}$$

Equation 6

Because ES only considers extreme limits of sway angle, it cannot capture the complete sway history during a trial. Therefore, we calculated two additional sway-related outcomes, Root Mean Square (RMS) distance of the COP, and elliptic area approximation of COP. The RMS distance of the COP ($DIST_{RMS}$) is an indicator of variability in COP movement. It has been shown to be a reliable measure of postural equilibrium (A. C.H. Geurts, Nienhuis, & Mulder, 1993; Le Clair & Riach, 1996; Palmieri, Ingersoll, Stone, & Krause, 2002) and is sensitive to altered sensory inputs (Holme et al., 2007; Niam, Cheung, Sullivan, Kent, & Gu, 1999). $DIST_{RMS}$ was calculated using Equation 7:

$$DIST_{RMS} = \sqrt{\frac{1}{N}\sum_{1}^{N} RD[n]^2}$$

Equation 7

Where N is the total number of samples during a trial, N= 2000 and $RD[n]$ is the resultant distance (RD) vector of the COP as given below (Eq. 8):

$$RD[n] = \sqrt{COP_{AP}[n]^2 + COP_{ML}[n]^2}$$

Equation 8

In Eq. 8, COP_{AP} and COP_{ML} are the COP components in the Anterior-Posterior (AP) and Medial-Lateral (ML) directions, respectively. The mean values of the AP and ML components were subtracted from the COP vectors in every trial to eliminate any inconsistency due to foot placement across trials. The mean was calculated over the 20s, the period of the trial.

Additionally, an elliptic area approximation of the COP path was computed for each trial. This measure captures the changes in COP path during standing and has been utilized as an indicator of overall postural performance (Paillard & Noé, 2015). Following the method described in Schubert *et al.*, we calculated a 95% prediction ellipse based on the assumption that points in the COP scatter follow a Chi-square distribution (Schubert & Kirchner, 2014). The area of the ellipse was calculated using Equation 9:

$$area_{PE} = \pi ab$$

Equation 9

Where a and b were semimajor and semiminor axes of the confidence ellipse and they were estimated according to Equation 10:

$$a = \sqrt{\chi_2^2 . \lambda_1}\ b = \sqrt{\chi_2^2 . \lambda_2}$$

Equation 10

In Eq. 10, λ_1 and λ_2 are eigen values of the COP covariance matrix. χ_2^2 is the value of the Chi-square cumulative distribution with two degrees of freedom at probability level=0.95.

Lastly, any changes in weight symmetry were ascertained by calculating the percentage of the body weight placed on the prosthesis. The ground reaction forces from the force plate underneath the prosthetic foot were normalized to the sum of ground reaction forces from both feet, i.e., body weight.

Statistical analyses

A two-way ANOVA was conducted to examine the effects of stimulation mode (i.e., sensory neuroprosthesis active or inactive) and SOT condition on the means ± standard deviations of the outcome measures. Extreme outliers, defined as data points more than three interquartile ranges away from either the lower quartile or upper quartile, were removed from the analysis. Normality was assessed using Kolmogrov-Smirnov normality test for each cell of the design. Any statistically significant interactions between stimulation mode and SOT conditions were followed up by analysis of simple main effects to determine the impact of stimulation under specific SOT conditions. For the analysis of simple main effects, the statistical significance received a Bonferroni adjustment for the two stimulation modes and was accepted at the $p < .025$ level. If no interaction effects were found, we tested for the main effect of stimulation on the measured outcome. Because there were only two stimulation modes, no post hoc analyses were deemed necessary. For all other comparisons, we used two-tailed t-tests followed by Bonferroni adjustments if multiple paired comparisons took place. All the statistical analysis were performed using IBM SPSS Statistics Ver. 22 (IBM Corp.).

Results

Sensations elicited by the sensory neuroprosthesis

For both participants, stimulation was delivered via different contacts in the cuff electrodes implanted on the sciatic nerve. For LL01, when pressure was applied to the FSRs at a location corresponding to the first metatarsal and big toe of the prosthetic foot, electrical stimulation was delivered to evoke sensations perceived as arising from the missing forefoot (**Figure 38**). In response to pressure on the FSRs underneath the prosthetic heel, the neuroprosthesis elicited sensation perceived as originating in the missing heel. Similarly, for LL02, pressure to first metatarsal and toe FSRs triggered electrical stimulation, which elicited sensation related to the missing 1^{st} to 5^{th} metatarsal areas. In response to pressure on the heel FSRs, the neuroprosthesis elicited sensation perceived as arising from the missing heel and lateral ankle.

Effects of sensory stimulation on ES

A significant interaction between stimulation mode and SOT condition for ES was found in both participants (LL01: $p = .029$, LL02: $p < .001$). This suggests that the effect of stimulation on ES depended on SOT condition (**Figure 39**). For both participants, ES was significantly lower in condition six (vestibular and somatosensory inputs compromised) during trials with the sensory neuroprosthesis active. For participant LL02, sensory feedback also led to an improvement in ES for conditions four (somatosensation compromised) and five (vision and somatosensation compromised).

In SOT condition six, the ES values were 74.8±9.6 and 65.2±7.9 for the sensory neuroprosthesis active and inactive, respectively, for LL01. This represents a statistically significant mean improvement of 9.2 with 95% Confidence Interval (CI) between 5.4 to 12.9 ($p < .001$). For LL02, the ES significantly improved in conditions four, five, and six. Additionally, for LL02, the effect of electrically elicited sensory feedback on ES grew bigger from condition four to six, and approached able-bodied norms. In condition four, the ES values for LL02 were 79.6±4.0 and 74.3±7.5 for sensory stimulation on and off, respectively, a statistically significant mean improvement of 5.2 (95% CI 0.2 to 10.3, $p = .042$). In condition five, the ES values for LL02 were 96.7± 5.7 and 63.4±7.1 for the sensory neuroprosthesis active and inactive, respectively, a statistically significant mean improvement of 6.3 (95% CI 1.3 to 11.3, $p = .015$). In condition six, the ES values for LL02 were 65.3± 4.0 and 49.7±13.7 for sensory stimulation on and off, respectively, a statistically significant mean improvement of 15.6 (95% CI 10.6 to 20.7, $p < .001$).

There was a statistical difference in baseline ES values without electrically elicited sensory feedback between LL01 and LL02 in conditions four, five, and six. In condition four, without sensory stimulation, the ES values were 84.0±6.8 and 74.4±7.1 for LL01 and LL02, respectively (p=.006). In condition five, they were 72.9±4.1 and 63.4±6.8 for LL01 and LL02, respectively (p=.001). In condition six, they were 65.1±7.5 and 49.7±13.1 for LL01 and LL02, respectively (p=.004). Such differences between the two participants suggest that without the sensory neuroprosthesis active, LL01 had higher postural stability than LL02 in the last three conditions of the SOT. Lastly, the ES from these two participants were compared to previously reported aged-matched normative ES values [45]. For conditions four, five, and six, LL02 had significantly lower ES without sensory stimulation (p < .05) whereas LL01 either scored equal or higher than normative values (**Figure 39**).

Effects of sensory stimulation on RMS distance of COP

Sensory stimulation affected the $DIST_{RMS}$ in both participants, as shown in **Figure 40**. For both LL01 and LL02, there was a statistically significant interaction between stimulation mode and SOT condition on $DIST_{RMS}$ (LL01: p < .001, LL02: p = .001). For both participants, $DIST_{RMS}$ was significantly lower in condition six during trials with electrically elicited sensory feedback. For LL02 only, $DIST_{RMS}$ also improved with sensory stimulation in condition four.

For LL01 in SOT condition six, the $DIST_{RMS}$ were 1.3±0.4 cm and 2.1±0.4 cm for the sensory neuroprosthesis active and inactive, respectively, a statistically significant mean difference of 0.8 cm (95% CI 0.6 cm to 1.1 cm, p < .001). Similarly, for LL02, the

$DIST_{RMS}$ during condition six were 2.0±0.4 cm and 2.9±0.7 cm for sensory stimulation on and off, respectively, a statistically significant mean difference of 0.8cm (95% CI 0.5 cm to 1.1 cm, $p < .001$). Additionally, for LL02, the $DIST_{RMS}$ in condition four was 1.1±0.2 cm and 1.4±0.4 cm for electrically elicited sensory feedback on and off, respectively, a statistically significant mean difference of 0.3 cm (95% CI 0.1 cm to 0.6 cm, $p = .018$). In condition four, the RMS distances without sensory feedback were 0.9±0.4 cm and 1.4±0.4 cm for LL01 and LL02, respectively. This suggests that without sensory stimulation, LL02 had higher sway compared to LL01 ($p=0.008$) which might have contributed to the sensory stimulation effect seen for LL02 in condition four.

Effects of sensory stimulation on area of prediction ellipse

We also found statistically significant interactions between stimulation mode and SOT condition for the area of prediction ellipse in both participants (LL01: $p = .003$; LL02: $p < .001$) that paralleled those for $DIST_{RMS}$ (**Figure 41**). For both participants, the area was significantly lower in condition six during trials with the sensory neuroprosthesis active. For participant LL02, electrically elicited sensory feedback also led to an improvement in condition four.

In SOT condition six for LL01, the areas of the prediction ellipses were 9.3±5.4 cm^2 and 18.5±2.0 cm^2 for the sensory neuroprosthesis active and inactive, respectively. This represents a statistically significant mean difference of 9.2cm^2 (95% CI 5.4cm^2 to 12.9 cm^2, $p < .001$). Similarly, for LL02 in condition six, the mean areas of the prediction ellipses were 18.1±6.4 cm^2 and 38.6±18.2 cm^2 for electrically elicited sensory feedback on and off, respectively. This represents a statistically significant mean difference of

20.5cm^2 (95% CI 14.6 cm^2 to 26.4 cm^2, $p < .001$). In addition to condition six, LL02 exhibited a significant difference prediction ellipse area in condition four. In this condition the mean areas of the prediction ellipses were 5.6±2.2 cm^2 and 12.5±8.4 cm^2 for sensory stimulation on and off modes, respectively, with a statistically significant mean difference of 6.93 cm^2 (95% CI 1.03 cm^2 to 12.84 cm^2, $p = .027$). Without the sensory neuroprosthesis active, the area of prediction ellipse under SOT condition four was 6.1±4.3 cm^2 and 1.4±0.4 cm^2 for LL01 and LL02, respectively. This suggests LL02 had much higher fluctuations in his sway compared to LL01 (p=0.01) without sensory stimulation.

Effects of sensory stimulation on weight symmetry

There was no statistically significant interaction between stimulation mode and SOT condition on body weight percentage on the prosthesis (LL01: $p = .809$; LL02: $p = .571$). However, the follow up analysis of the main effect for stimulation revealed a statistically significant effect of stimulation across all conditions. During trials with the sensory neuroprosthesis active, participant LL02 increased the percentage of his body weight on the prosthesis by 2% (95% CI 1.1% to 2.8%, $p < .001$) (**Figure 42**). These results suggest that LL02 shifted more weight onto his prosthesis when he received sensory stimulation regardless of SOT condition. The follow up analysis of the main effects did not show any changes in body weight distribution between sensory stimulation modes for LL01 ($p = 0.22$).

Discussion

In this study, we demonstrated that sensations elicited in the missing foot of two transtibial amputees could decrease sway and improve balance when vestibular input and somatosensation in the intact foot were compromised. The sensations in the missing foot were elicited using a sensory neuroprosthesis that electrically activated nerves in the residual limb via implanted non-penetrating nerve cuff electrodes. The location and intensity of perceived sensations were determined and modulated according to prosthetic foot-floor contact pressure. Using this approach, we were able to examine the role of plantar somatosensory feedback from the missing foot during standing balance under challenging, dynamic conditions.

In both participants we observed that the information from the sensory neuroprosthesis was most useful during condition six of the SOT, during which vestibular inputs and somatosensation in the intact leg were simultaneously perturbed. This improvement was seen in all three balance measures (ES, $DIST_{RMS}$, and area of predicted ellipse), which demonstrates that not only were the maximum boundaries of sway reduced, but participants also remained steadier throughout the entire trial period with the neuroprosthesis active. Consistent with previous reports of naturally occurring sensory inputs, our findings show that participants utilized the most reliable sources of sensory information when others were compromised (Fay B. Horak et al., 1989), including the perceptions of plantar sensation elicited by neural stimulation.

Our results confirm that LLAs adapt to lack of sensory input from their missing limb in part by relying on sensation from the intact leg. For LL02, we found the ES decreased during all three conditions (#4-6) that perturbed somatosensation in the intact foot. A prior study showed that poor perception of vibration and pressure in the intact foot and ankle was associated with poor static and dynamic balance in dysvascular transtibial amputees (Quai et al., 2005). Moreover, it has been reported that LLAs use their intact limb to obtain sufficient sensory information for function (Claret et al., 2019; Quai et al., 2005). In a study by Miller *et al.*, the number of reported falls per year for bilateral amputees was more than double that of unilateral amputees, suggesting that the loss of sensory input from both legs drastically increases fall risk (William C. Miller, Deathe, et al., 2001). These observations suggest that sensory neuroprostheses may be the most beneficial for LLAs with poor intact limb sensation.

The differences in the effect of the sensory neuroprosthesis on outcome measures between the two participants can be explained mainly by how they prioritized other sensory inputs. LL01 also had equal or better ES compared to age-matched able-bodied controls, an indicator of good balance stability among traumatic transtibial amputees (Hermodsson et al., 1994; Vanicek et al., 2009). Furthermore, LL01 was more stable without sensory stimulation in conditions four and five compared to LL02, which signifies that he may not have needed the additional sensory feedback as much and therefore did not utilize it in those conditions. However, LL02 found himself in a less stable situation; therefore, the electrically elicited sensory feedback resulted in an improvement in balance during the same conditions. Other factors such as residuum length (Gaunaurd, Gailey, Gomez-Marin, Kirk-Sanchez, & Hafner, 2011) and choice of prosthetic foot (Nederhand et al., 2012) could have contributed to differences seen between two participants. Additionally, the amplitude for the surround and the platform movements during the SOT was chosen based on the confidence of each individual in controlling their balance. The difference in balance confidence between participants may also explain better sway measures for LL01 without the sensory neuroprosthesis active.

Maintaining balance is a complex sensorimotor function, which requires central processing of multiple sensory inputs at the vestibular nuclei (Vouriot et al., 2004). The CNS compares the sensory inputs against an internal model and attributes relative weights to them to generate appropriate motor responses (Mergner, Huber, & Becker, 1997). With reduced or conflicting sensory information, the motor performance is directly affected, and balance stability may subsequently become compromised (Peterka & Black, 1990). In LLAs, not only is the sensory information from the missing foot absent, but also the internal body model has changed as a result of the altered neuromuscular and sensorimotor systems following amputation (Alexander C.H. Geurts & Mulder, 1992). For example, it has been shown that plantar pressure sensations are used to update internal estimates of center of mass location, which is a key factor in balance stability (Meyer, Oddsson, & De Luca, 2004; Morasso & Schieppati, 1999). It is possible that the internal models of the participants in this study were updated after the first use of the sensory neuroprosthesis. Future studies should consider baseline measurements of balance prior to providing any electrically evoked somatosensations to LLAs to investigate if updates to internal model contribute to observed improvements in balance. Alterations in the internal model by prior exposure to sensory stimulation would further support the implications that the intact neuromuscular balance control apparatus interprets the electrically elicited sensations in a similar manner to naturally occurring sensory inputs, and utilized them effectively to help maintain standing balance and stability.

The sensory neuroprosthesis appeared to improve body weight symmetry in LL02 but it did not have any significant effects on weight distribution in LL01. This finding confirms that weight symmetry in LLAs could be affected by loss of sensation, however other variables such as prosthetic alignment, prosthetic foot design, socket fit, and even poor hip abductor muscle strength could play a role in this outcome measure (Andres & Stimmel, 1990; Nadollek et al., 2002; Snyder, Powers, Fontaine, & Perry, 1995). Moreover, several studies have shown that weight symmetry in LLAs is regained within eight weeks after first prosthesis use, and in many cases there is not much improvement beyond this period (Nederhand et al., 2012; Stolov, Burgess, & Romano, 1971). Since the participants were long-term prosthesis users, their no-stimulation baseline symmetry values should have stabilized. Similarly, they were both exposed to sensory stimulation in the laboratory for a year prior to these experiments, thus the symmetries exhibited with the neuroprosthesis should have also plateaued. The time course of changes in symmetry due to the sensory neuroprosthesis can be the topic of future exploration. Lastly, sensory feedback affected sway measures differently than weight symmetry, suggesting that improvements in balance are not always correlated with a more symmetrical weight distribution (Nederhand et al., 2012).

It is likely that participants used the pressure exerted by the prosthetic socket on the residual limb to obtain information regarding movements of the support platform, and their own sway behaviors. However, the feedback through the socket and residuum is often not refined enough to compensate for the missing plantar sensation (Quai et al., 2005). Additionally, sensory feedback through the socket can vary based on changes in skin sensitivity (W. C. Lee, Zhang, & Mak, 2005), residual limb volume (Beil, Street, &

Covey, 2002), liner material (Al-Fakih, Abu Osman, & Mahmad Adikan, 2016), and alignment (Jia, Suo, & Wang, 2007). Furthermore, in dysvascular amputees, sensation through the socket could be limited due to diminished sensation in the residual limb due to the primary disease process (Hermodsson et al., 1994).

Although participants reported proprioception around the ankle during threshold and mapping experiments with our sensory neuroprostheses (Charkhkar et al., 2018), they do not report proprioception when postural expectations are incongruent, i.e. when standing upright with a fixed prosthetic ankle. In this scenario, the participants are consciously aware that the ankle is locked; therefore, the elicited sensations are reported as muscle tightening around the ankle or perceived as contractions of the calf muscles. Future effort will focus on integrating the sensory neuroprosthesis with volitionally controlled prosthetic ankles, so that the ankle joint is a part of the sensory neuroprosthesis and participants can benefit from elicited proprioception in addition to plantar pressure sensation.

In able-bodied individuals, three main motor strategies are utilized to maintain balance during static and dynamic conditions (Barnett et al., 2013). Movements at the ankle (i.e., the ankle strategy) are in response to small perturbations. Movements at the hip (i.e., the hip strategy) are often used to compensate for large perturbations. If there is a sudden change in the base of support in relation to the COG, then a stepping strategy is utilized to maintain balance (Maki & McIlroy, 1997). Because transtibial amputees are missing an ankle joint, they often use the hip joint to stabilize their COG in response to small perturbations of balance (Eakin, Quesada, & Skinner, 1992; Kamali, Karimi, Eshraghi, & Omar, 2013). In this case, accurate sensory feedback is still required to activate proper trunk rotation around the hip joint to maintain stability. However, if LLAs could control their prosthetic ankle joint to generate sufficient moment in response to sensory input, even greater improvements in balance could be expected from integrating a sensory neuroprosthesis with an active ankle.

The results of the experiments described here were based on limited use of a sensory neuroprosthesis in the laboratory environment. It is possible that with continuous use of a sensory neuroprosthesis at home and in the community, amputees could learn to rely on the new somatosensory input and use it more effectively in controlling balance. LLAs depend on visual feedback or upper extremities in controlling their posture during the early stages of post amputation rehabilitation (Alexander C.H. Geurts & Mulder, 1992). However, such dependency reduces over time as they learn to utilize the somatosensory information available through the intact limb and socket. A sensory neuroprosthesis may have the potential to reduce initial dependency on the intact limb, and accelerate progress through post-amputation rehabilitation.

Although participants in this study were transtibial amputees, other populations such as transfemoral amputees and elderly people exhibit comparable sensorimotor characteristics, which predisposes them to an increased risk of fall (Vanicek et al., 2009). It has been reported that when any two sensory inputs are simultaneously compromised in elderly people, a significant increase in sway occurs (Peterka & Black, 1990; M. H. Woollacott, Shumway-Cook, & Nashner, 1986). As such, providing neural sensory stimulation to those who have compromised sensory perception in their lower limbs could be an effective way to improve standing stability in multiple user populations.

Conclusions

The functional benefits of a sensory neuroprosthesis for improving standing balance were documented by computerized dynamic posturography in two individuals with transtibial limb loss. Appropriately localized and modulated sensations of plantar pressures under the prosthetic foot were elicited by delivering stimulating currents directly to the nerves in the residuum via multi-contact non-penetrating cuff electrodes. We demonstrated these elicited sensations were integrated into the intact neuromuscular control system to reduce sway and increase stability in terms of variations in center of pressure and Equilibrium Scores during perturbed standing. Symmetry of the loads applied to the intact and prosthetic legs was also significantly improved with the information provided by the sensory neuroprosthesis. The sensory neuroprosthesis had the strongest impact on maintaining balance when other resources, such as vision, vestibular, or somatosensory inputs from the intact leg, were compromised. These findings indicate that the information provided by a closed-loop sensory neuroprosthesis employing implanted neural stimulation technology was processed by the central and peripheral nervous systems as if they arose from the missing limb to positively impact standing balance. The generalizability of these results on a larger sample of LLAs, and their implications on daily function in uncontrolled home and community environments, their impact on the incidence and risk of falls and losses of balance, and the potential benefits of integrating sensory stimulation with active or semi-active microprocessor controlled prosthetic ankle or knee joints remain to be determined.

Figure 36: *Conditions of SOT in which controlled perturbation to visual, vestibular, and somatosensory inputs could be applied.*

Red boxes denote perturbation of the corresponding sensory input. Participant's eyes were closed in conditions 2 and 5.

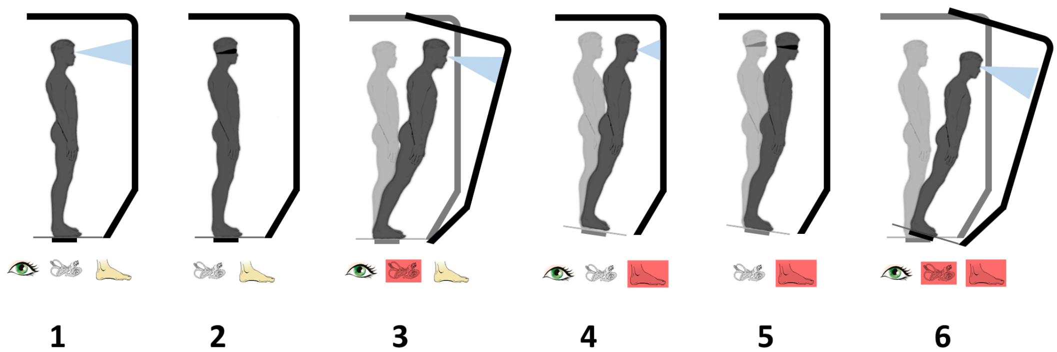

***Figure 37:** Illustration of implanted system and its components.*

The cuff electrodes were implanted on sciatic and/or tibial and peroneal nerves. The access to individual contacts within each cuff electrode was through percutaneous leads which connected to an external stimulator.

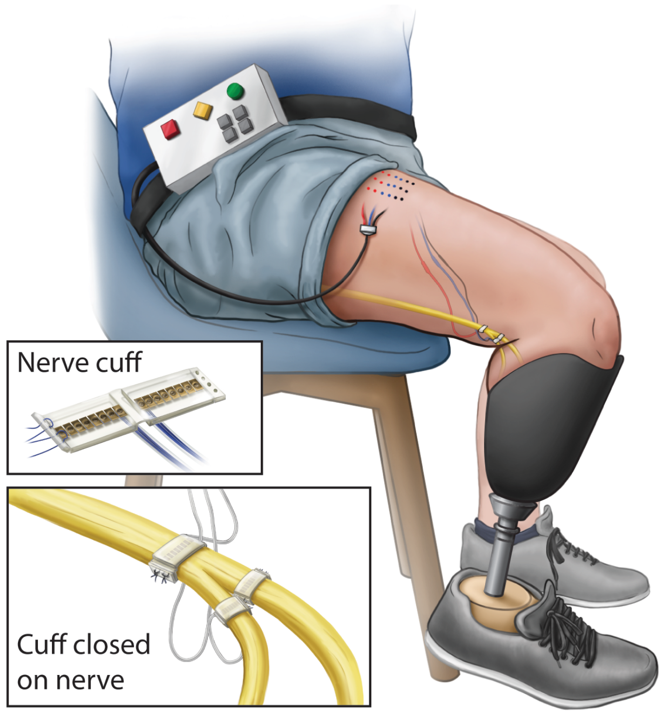

***Figure 38:** Reported percept locations from LL01 and LL02 used in the SOT.*

Stimulation delivered selectively to contacts generating perceived sensations referred to the missing toes and heels in response to pressures applied to the insole FSR array.

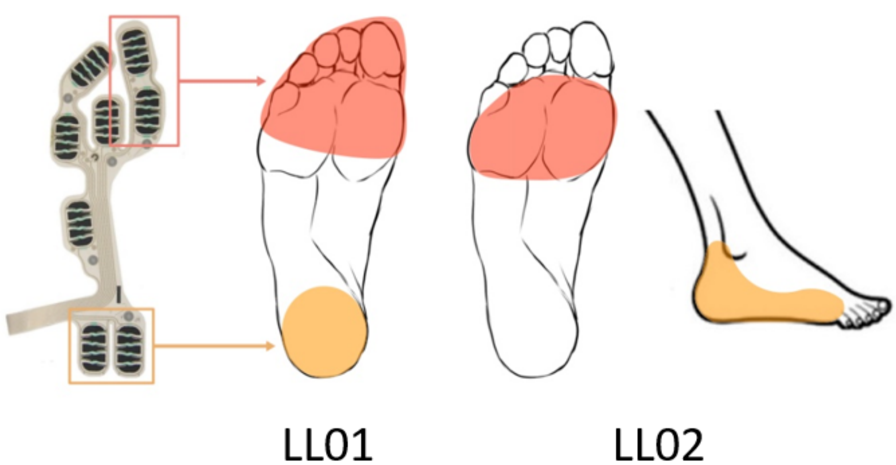

Figure 39: *Effects of sensory stimulation on SOT Equilibrium Score for LL01 (top) and LL02 (bottom).*

Age-matched normative means are shown in red. There was a significant interaction between stimulation mode and SOT condition. For LL02, the ES was improved with sensory feedback in conditions four, five, and six. For LL01, this improvement was observed in condition six. * and ** denote $p < .05$ and $p < .001$, respectively.

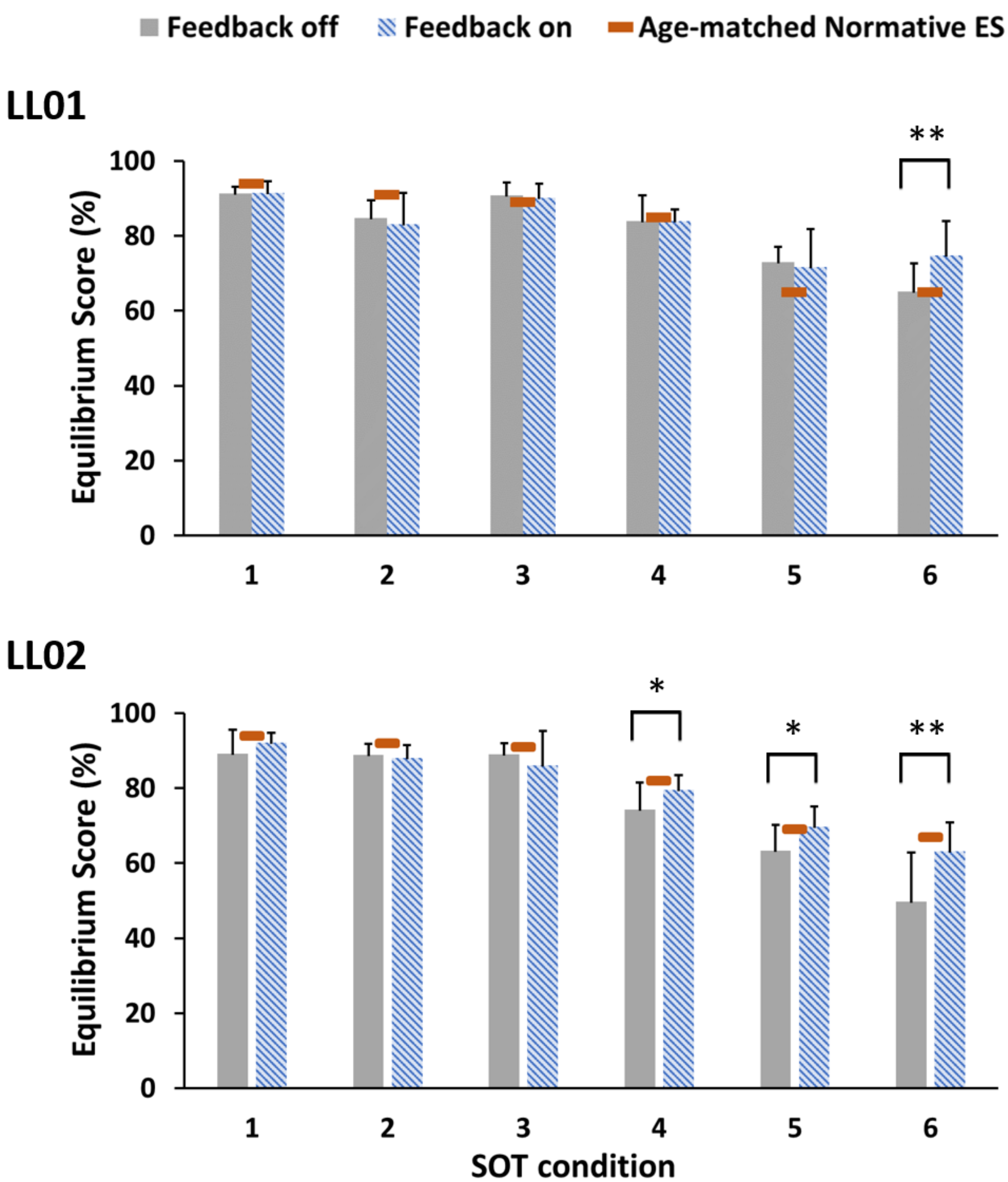

Figure 40: *Effects of sensory stimulation on RMS distance of COP for LL01 (top) and LL02 (bottom) in the SOT.*

There was a significant interaction between stimulation mode and SOT condition. For LL01, the RMS distance of the COP was reduced with sensory feedback in condition six, indicating improved balance. For LL02, the reduction in RMS distance of COP was observed in conditions four and six. * and ** denote $p < .05$ and $p < .001$, respectively.

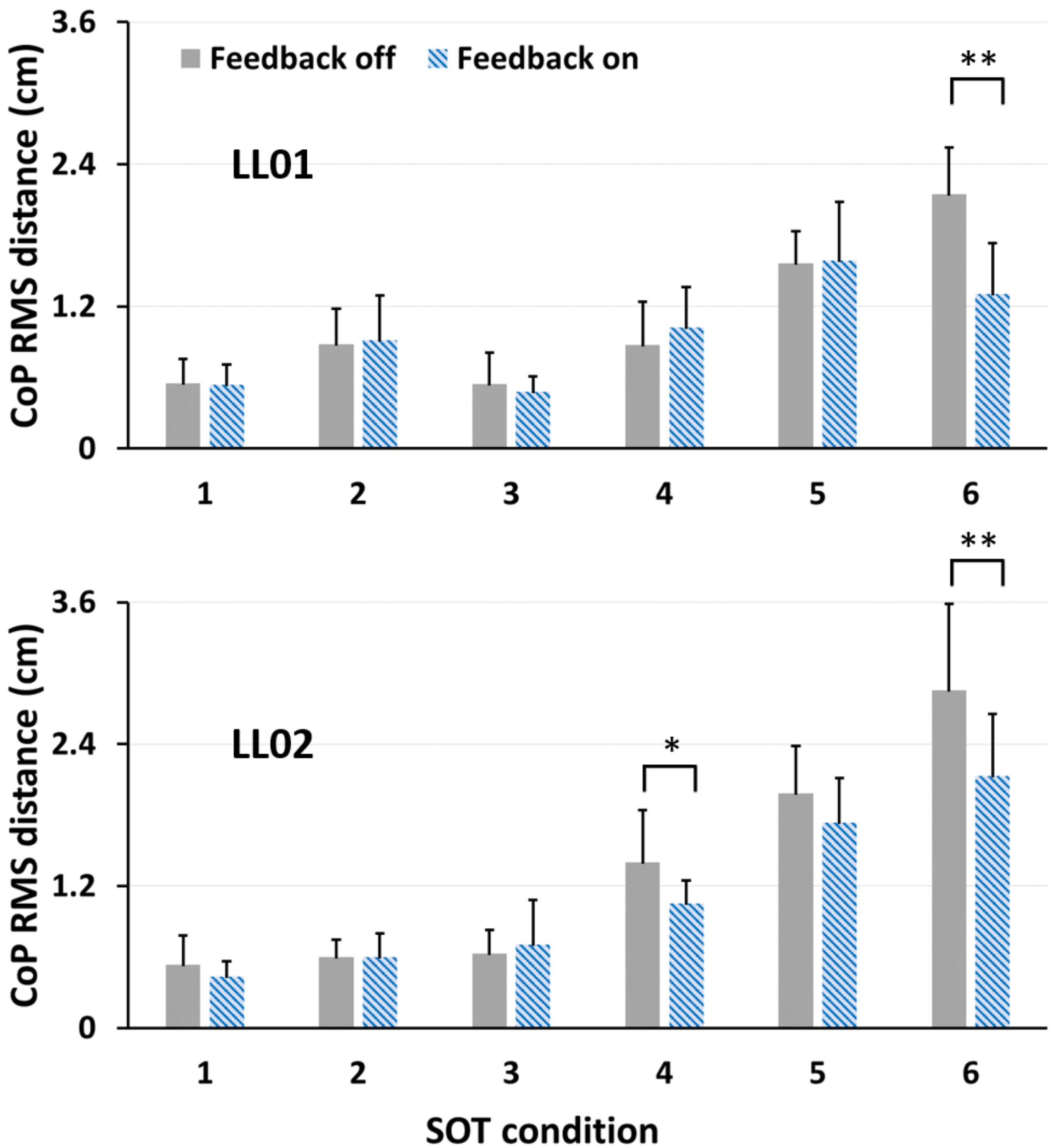

Figure 41: *Effects of sensory stimulation area of prediction ellipse for LL01 (top) and LL02 (bottom) for the SOT.*

There was a significant interaction between stimulation mode and SOT condition. For LL01, the area of prediction ellipse was reduced with sensory feedback in condition six, suggesting an improvement in balance. For LL02, the reduction in the area of prediction ellipse was observed in conditions four and six. * and ** denote p < .05 and p < .001, respectively.

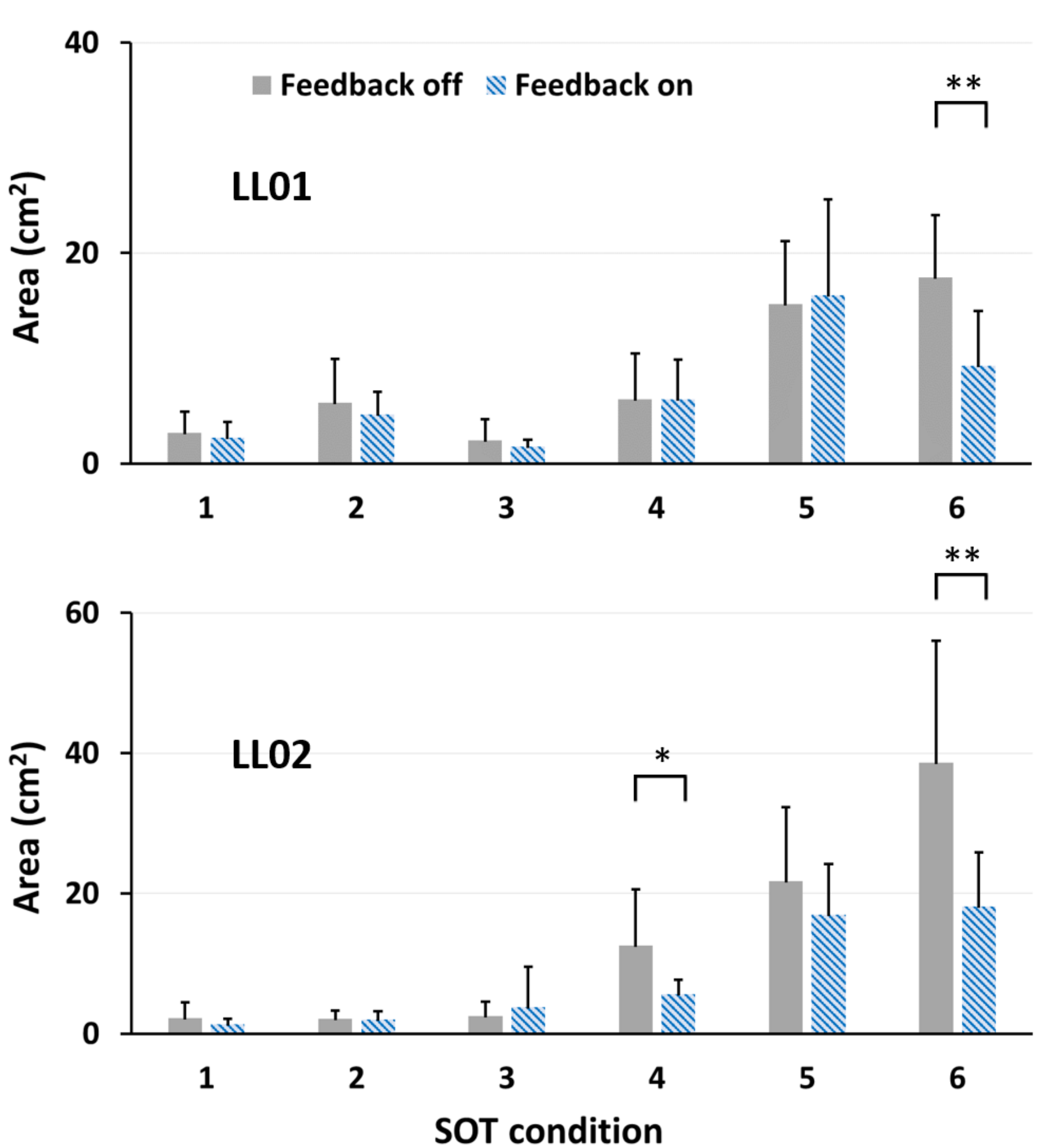

Figure 42: Overall effects of sensory stimulation on weight symmetry across all SOT conditions.

No significant interaction between stimulation mode and SOT condition were found on weight symmetry. However, there was a statistically significant effect of stimulation on weight symmetry regardless of SOT condition for LL02. ** denote p < .001.

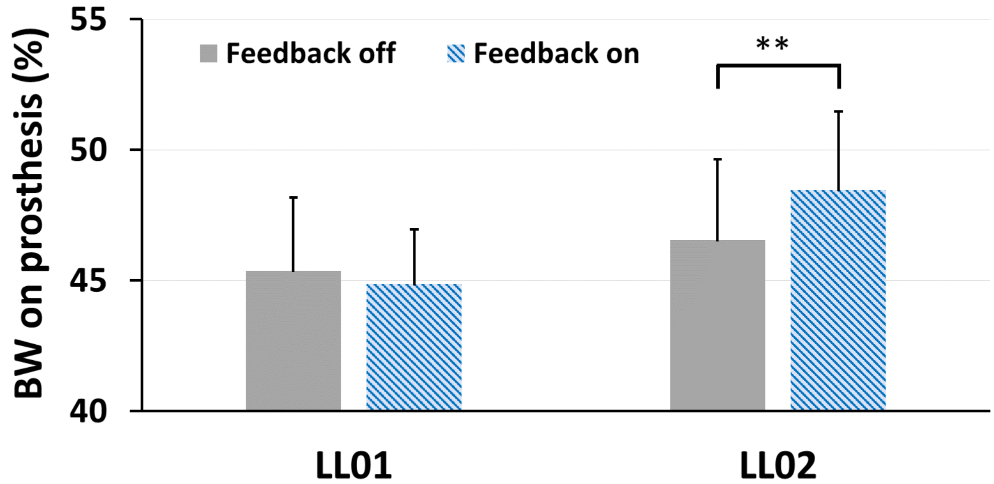

Table 16: Summary of participant characteristics enrolled in the SOT study.

Participant	Sex	Age (year)	Height (cm)	Weight(kg)	Amputated side	Etiology	Time since amputation
LL01	M	67	173	106	Left	Traumatic	48
LL02	M	54	168	67	Right	Traumatic	11

Table 17: Summary of conditions in a SOT.

Condition	Platform	Eyes	Surrounding
1	Stationary	Open	Stationary
2	Stationary	Closed	Stationary
3	Stationary	Open	Moving
4	Moving	Open	Stationary
5	Moving	Closed	Stationary
6	Moving	Open	Moving

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