Synaptic coupling of single cutaneous afferents of the median nerve with ankle muscles, and their discharge characteristics to rapid light touch displacements

by

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Abstract

Lightly touching a stable reference can greatly improve balance. Unexpected displacement of a light touch reference at the finger can lead to rapid activation of ankle muscles in standing participants and transcutaneous electrical stimulation of the median nerve generates short latency reflexes in ankle muscles. Together, this evidence suggests that cutaneous afferents in the hand are functionally coupled with the ankle muscles and might be involved in generating these interlimb balance responses, however the specific afferents serving these responses is unknown. For this thesis I wished to delineate the specific cutaneous afferents from the hand that mediate these interlimb responses. Specifically, it was hypothesized that activity of individual cutaneous afferents of the median nerve innervating the hand will modulate the electromyographic (EMG) activity of ankle muscles at short (<120 ms) latencies. It was also hypothesized that type I cutaneous afferents of the hand will show a distinct increase in firing frequency during a rapid displacement of a light touch contact across their receptive field. To investigate these hypotheses, this study was performed in two parts. In all experiments, microneurography of the median nerve at the level of the wrist was used to record discretely resolved fast and slow adapting type I and II (FAI, FAII, SAI, and SAII) afferents from 18 and 9 participants in Part one and two of the study respectively. In Part one, the discharge from discretely resolved afferents was used for generating spike-triggered average surface EMG traces of the bilateral tibialis anterior (TA) and soleus (SOL) muscles. Responses were identified when the averaged EMG trace exceeded a 99% confidence band, calculated from the background EMG activity, for a minimum of ≥ 2.5 ms. In Part two, twenty alternating touch contact displacements

(1.25 cm displacement, 120 ms duration), ten away from the participant and ten towards, were delivered across the receptive fields of the identified afferent. The firing characteristics were qualitatively compared across the afferent types. Over 55 experiments, 53 single afferents were recorded and used for subsequent analysis, 42 in Part one and 11 in Part two. From Part one, 34/42 (81%) of the individual cutaneous afferents recorded produced demonstrable responses in the spike-triggered average EMG trace at latencies <120 ms. All afferent types demonstrated responses in both TA and SOL, with a bias of observed responses towards the early latency epoch (40-80 ms) in TA. In Part two, 11 individual cutaneous afferents were recorded, and our second hypothesis was partially supported as we demonstrated that type I and II afferents in the glabrous skin of the hand become active and remain more active than baseline throughout the rapid displacement of a light touch contact across its receptive field. These results suggest that cutaneous afferents in the hand consistently form interlimb connections with muscles of the lower limb at latencies implicating spinal-mediated pathways, and the same population of afferents are readily excited by a rapid displacement of a light touch contact. Therefore, cutaneous afferents in the hand can be recruited and utilized to alter motoneuron pool excitability in muscles important to balance control, at latencies relevant for balance corrective responses.

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Introduction

Standing is a mechanically challenging task for humans. Normally, humans assume a bipedal stance, which places the body center of mass (COM) relatively high (Winter, Patla, & Frank, 1990) above a proportionally small base of support (Pollock, Durward, Rowe, & Paul, 2000). Consequently, maintaining stable standing requires a great deal of control. Failing to manage this balancing act can result in a devastating fall. Consequences can range from superficial wounds to hip or ankle factures, and even brain injury (Hartholt et al., 2011). Each year there are approximately 37.3 million falls that require medical attention globally (WHO, 2018). The prevalence of falls is likely to increase as well, as age is a risk factor in falling (Spaniolas et al., 2010), and the elderly are the fastest growing age group world-wide (Coimbra, Ricci, Coimbra, & Costallat, 2010). In Canada alone, from 2017 – 2018 hospitalization from falls increased 9%, and accounted for 81% of all hospitalizations involving seniors (Canadian Institute for Health Information, 2019). Additionally, the financial costs of falls are large, from 2000 – 2001 in Canada there was an estimated $911 million in hospital costs associated with falls (Canadian Institute for Health Information, 2002).

Balance control is multifactorial, involving many systems to detect and correct any loss of balance, and at any stage an incorrect response can result in a fall. The central nervous system (CNS) is responsible for maintaining upright balance, accomplishing this through both 1) proactive control in anticipation of impending challenges, and 2) reactive control in response to unexpected disturbances (Patla, 1993). This complex control of balance requires integrated, whole-body motor strategies to be implemented within the context of other ongoing tasks while also accounting for any environmental or contextual constraints (Marigold & Misiaszek, 2009). Sensory information is critical to not only detect when the body is out of balance, but also the context, environment, and actions of the body that challenge equilibrium. The sense of balance, or equilibrioception (Macpherson 2011) incorporates feedback from multiple sensory systems, including visual, vestibular, and somatosensory.

Visual information contributes to balance control by indicating spatial orientation relative to the environment (Amblard & Carblanc, 2011; Merla & Spaulding, 1997), where self-movement is inferred against objects interpreted as stationary. By removing visual feedback, like closing one’s eyes, there is a significant increase in antero-posterior sway area and velocity when standing (Howcroft, Lemaire, Kofman, & McIlroy, 2017). The vestibular system is sensitive to both linear and angular accelerations of the head (Fitzpatrick & Day, 2004), indicating if the head is moving, tilting, or translating through space. In addition, the vestibular apparatus is sensitive to the continuous acceleration of gravity, which provides information about the orientation of the head in space as well as the orientation of the head relative to gravity’s pull, providing an earth-referenced spatial orientation (Day & Fitzpatrick, 2005), used in balance control (Horak, 2006). Additionally, by using galvanic vestibular stimulation, virtual head movements are signalled and organized, whole-body balance responses can result (Fitzpatrick & Day, 2004). Evidently, the visual and vestibular systems play a large role in balance control, sensing equilibrium, with balance responses organized to reflect their sensory input.

Along with the visual and vestibular systems, there is a third sensory input, the somatosensory system; which contributes importantly to balance control in two ways: via proprioception and touch. Proprioception is the signalling of the position of the limbs in space. Muscle spindles and Golgi tendon organs are muscle-based sense organs that detect changes in muscle state (e.g. muscle length or muscle tension) that can provide important signals related to upright posture and balance (Hulliger, 1984; Hulliger, Dürmüller, Prochazka, & Trend, 1989; Jami, 1992). Several lines of research have investigated the role of muscle-based sense organs in balance control including: rapid muscle stretches (Jones & Watt, 1971), support surface tilts (Aniss, Diener, Hore, Gandevia, & Burke, 1990) and translations (Nashner, 1977), as well as tendon vibration (Eklund, 1972; Roll & Vedel, 1982; Thompson, Bélanger, & Fung, 2007). It is clear from these studies that muscle-based sense organs are important sources of sensory information for both the rapid detection of unexpected balance disturbances, but also the steady-state control of otherwise stable balance. In addition to the muscle-based somatosensory organs, skin-based, low threshold cutaneous mechanoreceptors have also been implicated in detecting joint position (Collins & Prochazka, 1996; Collins, Refshauge, Todd, & Gandevia, 2005), presumably by the contribution of differential skin stretch across a joint (Hulliger, Nordh, Thelin, & Vallbo, 1979). However, low-threshold cutaneous mechanoreceptors are also the primary sense organs involved in touch sensations, which are well documented to contribute to balance control (Chen & Tsai, 2015; Holden, Ventura, & Lackner, 1994; Jeka, 1997; Jeka & Lackner, 1994; Meyer, Oddsson, & De Luca, 2004; Winter, 1995). The contribution of touch to balance control is the focus of this thesis and will be elaborated in the subsequent paragraphs.

Low threshold cutaneous mechanoreceptors are highly sensitive in detecting mechanical changes of the skin, like physical touch, and this ability has been shown to contribute to balance control from both the upper (Jeka & Lackner, 1994) and lower limbs (Meyer et al., 2004; Winter, 1995). In the upper limb, it was found that fingertip cutaneous feedback from a stable reference point can reduce postural sway (Holden, Ventura, & Lackner, 1994; Jeka & Lackner, 1994), without providing additional mechanical support (Kouzaki & Masani, 2008). The discovery that small forces at the fingertip can influence balance control utilized a light touch paradigm; in this set-up, participants typically stand in an unstable position with vision occluded, touching a surface with the tip of the finger with less than one newton of vertical force. Light touch studies have demonstrated several longer latency behavioral findings, linking cutaneous feedback at the hand to a role in balance control (Dickstein, Shupert, & Horak, 2001; Jeka, Oie, Schöner, Dijkstra, & Henson, 1998; Wing, Johannsen, & Endo, 2011). The time course of these findings suggests a cortical and slower integrative route for cutaneous input at the finger to be incorporated into balance control.

Recently there has also been evidence that cutaneous input at the finger can influence balance control at short latencies therefore likely taking spinal routes. Misiaszek et al. (2016) demonstrated that when lightly touching a surface, a rapid and unexpected displacement of that surface can elicit balance corrective responses as early as 53.5 ms in muscles of the lower limb. These short-latency responses are argued to occur due to the cutaneous stimulation at the finger and share similarities with cutaneous reflexes evoked by electrical stimulation. For example, cutaneous reflexes can occur at short latencies (≤120 ms), are generated by stimulation of cutaneous afferents, and can be observed in muscles distant from the site stimulated (Delwaide & Crenna, 1984; Macefield, Rothwell, & Day, 1996; Zehr, Collins, & Chua, 2001). Cutaneous reflexes can be evoked with mechanical stimulation (Macefield et al., 1996), however, electrical stimulation is the preferred method (Delwaide & Crenna, 1984; Zehr et al., 2001) because of its robustness in eliciting responses. However, there are details lost when using transcutaneous electrical stimulation, such as the ability to discern any potential receptor dependent effects. Transcutaneous electrical stimulation will recruit most, if not all, sensory axons and will bypass the receptors themselves, eliminating the ability for receptors to transduce potentially critical information. As there are several types of low threshold mechanoreceptors, each with their own characteristics (Johansson & Vallbo, 1983), transcutaneous electrical stimulation is unable to discern any specific roles the different cutaneous receptor types might contribute to balance control or the rapid balance corrective responses observed by Misiaszek et al. (2016). In this thesis, I will use microneurographic recordings of single cutaneous afferents to further delineate the potential contribution of the different cutaneous receptor types to interlimb cutaneomuscular responses.

Microneurography is an electrophysiological technique that allows activity from single mechanoreceptor afferents to be recorded in awake human beings (Vallbo & Hagbarth, 1968). Using microneurography, single cutaneous mechanoreceptor afferents have been demonstrated to make intra- (Fallon, Bent, McNulty, & Macefield, 2005;

McNulty & Macefield, 2001; McNulty, Türker, & Macefield, 1999) and inter-limb (Bent & Lowrey, 2013) connections to muscles throughout the body. In these studies, it was also demonstrated that some afferent types showed a greater likelihood of demonstrating connectivity to some of the muscles recorded than others, suggesting functional specificity based on sensory modality. To date, interlimb connectivity of single cutaneous afferents of the hand to motor pools of leg have yet to be demonstrated, and the characteristics of the afferent types that might contribute to such connections have not been described. Finding evidence of this connection would suggest that cutaneous afferents in the hand are capable of contributing to functionally relevant balance corrective responses (Misiaszek et al., 2016).

The hands are utilized for many tasks, ranging from incredibly fine motor skills to discerning high-quality details from objects being handled. The vast capabilities of the hands are supported in part by the variety of sensory modalities and densities of low threshold cutaneous mechanoreceptors that exist within the hand. Specific afferent types have even demonstrated task-dependent differences in the transduction of critical information at specific phases of a motor task (Johansson & Westling, 1984; Westling & Johansson, 1984, 1987). It is therefore probable that some cutaneous modalities are preferentially activated in response to light touch stimuli involved in balance control or short-latency, interlimb balance corrective reactions. Moreover, these sensory modalities would then also likely demonstrate differences in the extent to which they form short-latency interlimb neural circuits with motor pools relevant to postural control at the ankles. Currently it is not known whether cutaneous afferents in the hand form such connections to muscles of the lower limb, or the pattern of activity cutaneous receptors show to a light touch displacement.

There is a multiplicity of sensory information collected for balance control and the somatosensory system plays a large role in this. The cutaneous component of the somatosensory system from the hand has demonstrated the ability to influence balance control in light touch experiments. Due to complexity of light touch effects, the uniqueness of the hand and the cutaneous receptors themselves, there may exist receptor specific effects. However, the role individual receptors may play in this connection has not yet been delineated. Therefore, my thesis research investigated the possible connectivity of single cutaneous afferents in the hand may form to muscles of the lower limb involved in standing balance, and how single afferents respond to a rapid displacement of a light touch contact across their receptive field. I hypothesized that activity from individual cutaneous afferents innervating the hand would modulate electromyography (EMG) activity in the ankle muscles, tibialis anterior (TA) and soleus (SOL), at short (<120ms) latencies. These latencies are consistent with previously studied interlimb cutaneous reflexes between the upper and lower limbs (Zehr et al., 2001), as well as latencies of balance corrective responses following the rapid displacement of a light touch reference (Misiaszek, Forero, Hiob, & Urbanczyk, 2016). I also hypothesized that type I cutaneous afferents of the hand will show a distinct increase in discharge frequency during a light touch displacement across their receptive field, whereas type II cutaneous afferents and afferents with a receptive field not directly stimulated by a light touch displacement will not exhibit a change in firing frequency.

This would be consistent with previous investigations that demonstrated increased firing frequencies in fast and slow adapting type I units in response to a localized slip (Johansson & Westling, 1987). By improving our knowledge of sensory-motor physiology in determining the role individual cutaneous afferents may play in light touch mediated effects on postural sway, technologies can be developed to aid in balance control, therefore creating possible benefits such as appropriate levels of sway for environmental exploration, ensuring the central nervous system receives a sufficient quantity of sensory information (Carpenter, Murnaghan, & Inglis, 2010) for balance control. These benefits could potentially translate to a decrease risk of falling in at risk populations and decrease the impacts of falls on the health of individuals and the associated burdens to the health care system.

Literature Review

Overview

This thesis investigates single cutaneous mechanoreceptors of the glabrous skin of the hand and potential excitability changes to muscles of the lower limb relevant to balance control, as well as how the same types of receptors respond to rapid light touch displacements across their receptive field. Previously, it was demonstrated that a rapid light touch displacement at the fingertip can elicit short latency balance corrective responses (Misiaszek et al., 2016), but it remains unknown which specific modalities elicit these responses. Therefore, the following literature review will briefly review the utility of the limbs in balance control, and the role of cutaneous feedback in relation to balance control. This is followed by a more in-depth review of cutaneous mechanoreceptors in the glabrous skin of the hand, the ability of these receptors to act through cutaneous reflexes, and the potential for these receptors to be involved in balance control and demonstrate receptor specificities.

The Hands and Feet in Balance Control

The hands and arms are often used in balance control, partly due to their large degrees of freedom and the motor strategies this affords. Coordinated arm movements are often used to reduce angular momentum after a perturbation (Roos, McGuigan, Kerwin, & Trewartha, 2008), or to reach for nearby objects for stability such as a handrail (Maki & McIlroy, 2006). The availability of the arms changes motor strategies used for balance correction. When perturbations are applied while walking, muscle responses in the lower limb can be enhanced when the arms are unavailable to aid correction (Misiaszek & Krauss, 2005), or removed when holding onto stable supports (Misiaszek, Stephens, Yang, & Pearson, 2000). Taken together, these findings highlight the mechanical interaction between the arms and legs in balance control and the impact this interaction can have on motor control strategies. However, the hands are also a rich sensory sheet and it has been suggested the sensory feedback they provide can facilitate balance control. For example, Rietdyk and Patla (1998) demonstrated that running a hand over a handrail while walking optimized the motor responses in the legs to unexpected perturbations. It was argued that cutaneous feedback from the hands provided information related to the interaction between the point of contact of the body (the hand) with the environmental support (the handrail), thereby providing input related to the motion of the body, as well as a spatial reference, and suggests that detection of shear forces may be an important signal in balance control. Previously, detection of shear forces at the hand have been shown to be critically necessary to adapt hand motor behavior in response to unexpected slip perturbations during a precision-grip task (Westling & Johansson, 1984). It is reasonable to anticipate that this powerful sensory cue, that links the interaction of the body with an interface to the environment, should also be integrated into balance control.

Indeed, shear forces at the foot have been argued to be critically important in balance control. Ting and MacPherson (2004), studying directional tuning of postural responses in standing cats, argued for a critical role of detection of “slip force” from the paws, analogous to slip detection in finger grip tasks in humans. In humans, the sole of the foot is richly endowed with cutaneous mechanoreceptors, comparable to what is seen in the hand (Strzalkowski, Peters, Inglis, & Bent, 2018). Moreover, the sole of the foot receives continuous cutaneous stimulation during the balancing tasks of standing and walking, as the foot is most often used as the base of support in these tasks. Consequently, there is a rich sensory contribution from cutaneous receptors in the feet that would seem logically to be relevant for detecting the state of the interface of the base of support (the feet) with the environment (the support surface). In fact, it has been shown that altering the amount of cutaneous feedback from the feet changes the motor strategies used to maintain balance. For example, diminished cutaneous feedback from the feet causes the primary balance corrective response during standing to change from a typical ankle strategy to the hip strategy (Meyer, Oddsson, and De Luca 2004; Horak, Nashner, and Diener 1990), which is normally associated with balance responses in more challenging environments. In addition, loading forces are also detected by cutaneous receptors and can provide valuable information about the interaction with the environment. For example, loading forces will detect the distribution of weight, and changes to this distribution, across the soles of the feet (Kavounoudias, Roll, & Roll, 1998), which can signal where the mass of the body is positioned, relative to the boundaries of the base of support. It has been argued that the relationship between the location of the body's mass and the position of the base of support is a critical parameter in balance control (Maki & McIlroy, 1997). Taken in total, there is a wealth of literature that indicates that cutaneous feedback, related to both shear and loading forces, contribute to equilibrioception and is used in balance control.

Light Touch Can Modulate Balance Control

Cutaneous sensitivity has varying degrees of resolution across the body, with a relatively high resolution in the glabrous skin of the hands, as a result of the types and densities of receptors in this area. Across the volar surface of the hand in the glabrous skin exists approximately 17,000 individual cutaneous mechanoreceptors (Johansson and Vallbo 1983). These receptors have a non-linear increase in density moving distally, resulting in over 1,000 receptors estimated to be concentrated in the tip of each finger distal to the vortex of the skin ridges (Johansson and Vallbo 1979). It has long been known that the high acuity for touch from the hands contributes to behaviors beyond the sensation of touch itself. For example, as early as 1895, Mott and Sherrington argued that cutaneous sensation was important for fine motor control when they observed that there was little functional loss in motor tasks when the arm was deafferented, so long as distal cutaneous innervation remained intact (Mott & Sherrington, 1895).

Cutaneous sensation from the hand has also been shown to influence postural control. Holden et al. (1994) found that lightly touching a stable reference point with a fingertip with less than 1 N of vertical force reduces postural sway. 1 N of force was originally chosen because it was argued to be too small to provide any mechanical support, and therefore only available to provide sensory cues about body sway (Jeka and Lackner 1994). Interestingly, forces <1 N cause the greatest change in the amount of skin deformation (Westling & Johansson, 1987), to which tactile units are extremely sensitive (Vallbo and Johansson 1984). Regardless, the provision of a light touch reference was shown to reduce postural sway as effectively as when vision was allowed or when mechanically supporting oneself with the fingertip touch (Holden, Ventura, & Lackner, 1994; Jeka & Lackner, 1994). Two arguments have been proposed to explain how lightly touching a stable reference affects postural sway. The first suggests that tactile information from the tip of the finger is functionally relevant, providing information about the body's position in space (Jeka 1997). Changes in position are sensed through changes in fingertip contact force and area and reacted to, thereby decreasing overall sway amplitude. In light touch experiments, modulating the cutaneous input has shown several distinct findings that would suggest the cutaneous drive is used in balance control. For example, postural sway entrains to an oscillating light touch surface (Jeka et al., 1998; Wing et al., 2011) with the changes in force at the fingertip leading sway by approximately 300 ms (Dickstein et al., 2001). In addition, removing cutaneous sensation from the hand eliminates the light touch effects on postural sway (Kouzaki & Masani, 2008). More recently, Misiaszek et al. (2016) demonstrated that an unexpected displacement of a touch reference evoked a rapid balance reaction, despite a lack of a mechanical threat to balance, implying that when the reference is expected to be stable the sensory feedback is incorporated into balance control. In summation, these studies indicate cutaneous inputs are required for the light touch effects and that the feedback leads the motor output, suggesting that tactile inputs are integrated into sway regulation and balance control.

In contrast, a second theory to explain the light touch effects on sway argues that the decreased sway is due to the task of maintaining a light touch. According to Riley and colleagues, maintaining a steady light touch transforms light touch experiments into a skilled task, wherein the motion of the body is constrained to maintain contact with the target surface (Riley, Stoffregen, Grocki, & Turvey, 1999). In fact, Bryanton et al. (2019) demonstrated that sway was reduced further if a light touch reference unexpectedly became unstable, suggesting that sway was constrained to enhance sensory acuity. Therefore, reduced sway during light touch studies might arise from the task constraints of the experimental paradigm, rather than integration of additional sensory inputs into the control system. However, in the study of Bryanton et al. (2019) sway increased if the participants were aware the touch reference was unreliable, suggesting that the higher control demand for maintaining contact in this context did not further reduce sway. Alternatively, sway reduction during light touch studies might reflect both an effect of the task constraint of maintaining contact and the integration of additional sensory input for greater resolution of the controlled parameter, with a balance between competing factors explaining the apparently disparate results.

Displacement of a Light Touch Surface Causes Short Latency Balance Corrective Responses

The Misiaszek group’s experiments using an unexpected light touch surface displacement demonstrate another key factor beyond evidence of a cutaneous drive for light touch impacting balance control, and that is the short latencies at which the balance corrective responses are observed. Balance reactions were typically seen in ankle muscles at about 100 ms, with some individuals responding as early as 53.5 ms, relative to the onset of touch surface displacement (Misiaszek et al., 2016). The short-latency of these responses suggest a subcortical or spinal pathway mediates the responses seen in the ankle muscles, as volitional reactions have latencies of approximately 140 ms (Macefield 2009). Cutaneous reflexes, evoked with transcutaneous electrical stimulation, in muscles throughout the body demonstrate onset latencies similar to the balance corrective responses observed by Misiaszek et al. (2016). Cutaneous reflexes are often described as having early (<75 ms), middle (75-120 ms), and late (>120 ms) components, with the most commonly observed being those in the middle latency epoch (Zehr, Collins, & Chua, 2001). Furthermore, cutaneous reflexes can be observed within the segment stimulated (intralimb), or in a segment distant from that stimulated (interlimb). Both intra- and interlimb responses occur at comparable latencies (Zehr et al., 2001) suggesting a common integrative route. Taken together, these results suggest that the short-latency balance corrective responses observed by Misiaszek et al. (2016) are spinal-mediated responses, that could utilize interlimb cutaneous reflex circuitry.

Cutaneous interlimb connections are well established in the literature. Animal work has shown ascending (Gernandt & Megirian, 1961) and descending (Skinner, Adams, & Remmel, 1980) interlimb cutaneous connectivity to muscles between the cervical and lumbar enlargements. These connections are thought to be mediated by propriospinal pathways within the spinal cord. The proposed functional argument behind these connections is to coordinate activity between the fore and hind limbs of quadrupeds. Although adult humans do not ambulate on all fours, bipedal locomotion does involve active coordinated use of the upper limbs (Kuhtz-Buschbeck & Jing, 2012), and balance corrections involve rapid whole-body coordinated activity, argued to be in part mediated through propriospinal pathways (Marigold & Misiaszek, 2009). Therefore, propriospinal networks may have a functional role in coordinating the actions of the fore and hind limbs, with cutaneous sensory information contributing to this coordination.

Transcutaneous Electrical Stimulation for Interlimb Cutaneous Reflexes

The existence of interlimb cutaneous reflexes in humans is well established and mirrors the circuitry described in animal work. Among the first to demonstrate cutaneous interlimb reflexes in humans were Delwaide and Crenna (1984) who demonstrated short-latency (~60 ms) changes in soleus H-reflex excitability, following electrical stimulation of the second and third digits of the hand using ring electrodes. In 2001, Zehr and colleagues demonstrated that interlimb cutaneous reflexes, arising from transcutaneous electrical stimulation of peripheral nerves, were observed in the ongoing EMG activity of muscles in both the arms and legs (Zehr et al., 2001). Importantly, interlimb reflexes were observed widely across the limb segments with onset latencies suggestive of propriospinal pathways. Zehr and Duysens (2004) subsequently argued that these pathways may be a substrate for coordinating the movements of the arms and legs, comparable to the functional role suggested in animal studies.

Transcutaneous electrical stimulation is a non-specific method of activating cutaneous reflexes, which therefore limits the understanding of the functional relevance of the findings. The stimulus utilized to evoke cutaneous reflexes in a laboratory setting uses trains of electrical stimulation at relatively high stimulus intensity. Normally, the stimulus intensities used to evoke cutaneous reflexes are two to three times the radiating threshold, which is the minimal stimulus intensity required to elicit paresthesia in the innervation territory of the stimulated nerve (Zehr, Komiyama, & Stein, 1997). At this stimulus intensity, transcutaneous electrical stimulation will recruit a broad array of sensory afferent axons, including all A_{β} afferents, but might also include group I or II proprioceptor afferents and some smaller diameter afferents. Therefore, cutaneous reflexes evoked in this manner lack specificity as to the type of afferents, and therefore sensory modality, contributing to the responses that are observed. In turn, this ambiguity limits the ability to ascribe functional interpretation of the findings. In addition, transcutaneous electrical stimulation activates afferents directly, bypassing the receptor end organelle. Consequently, any physical filtering and transduction that may contribute to the differential activation of modality specific cutaneous afferents in a more natural, behavioural setting is lost.

Single Cutaneous Mechanoreceptor Intra- and Interlimb Connectivity

To overcome the ambiguity in interpretation that arises with the use of electrical stimulation of peripheral nerves, some studies have instead used approaches using microneurographic recordings of single afferent axons. For example, using a method known as spike-triggered averaging (STA), it was found that single low threshold cutaneous afferents, arising from the glabrous skin of the hand, were able to modulate the ongoing EMG activity of muscles serving the same hand (McNulty & Macefield, 2001; McNulty et al., 1999). Importantly, the activation of the recorded afferents was triggered by natural, mechanical stimuli applied to the skin over the sensory territory of the identified cutaneous receptor. Similar *intralimb* connectivity has been demonstrated in the lower body between individual cutaneous afferents of the foot and muscles acting on the same foot (Fallon et al., 2005). In addition, this same approach has yielded evidence indicating that single cutaneous afferents form *interlimb* connections between limbs as well. For example, STA approaches have shown that activity of single mechanoreceptors in the skin of the foot was associated with modulation of ongoing EMG activity in muscles of the upper limb (Bent & Lowrey, 2013). The onset latencies of the interlimb coupling observed by Bent and Lowrey (2013) was comparable to the cutaneous reflex latencies that emerge with transcutaneous nerve stimulation (Zehr et al., 2001), indicating that the specific afferents studied with the microneurographic approach likely contribute to the whole nerve stimulation results. Moreover, this indicates that specific afferent activity, representing individual modalities of cutaneous sensory feedback, form functional interlimb connections at latencies that could contribute to the whole-body balance corrective responses observed following displacement of a touch reference (Misiaszek et al. 2016). However, such interlimb coupling between cutaneous afferents of the upper limb, to muscles of the lower has yet to be demonstrated. Furthermore, it is not known if receptor-specific differences in connectivity from the arm to the leg exist, that might indicate differential influences of specific sensory modalities in these functional connections. For example, Bent and Lowrey (2013) demonstrated that some afferents were more likely to form interlimb connections than others, suggestive of differential influences of specific receptor types.

Single Cutaneous Mechanoreceptor Afferent Characteristics

The cutaneous afferents recorded when investigating connections of single afferents to various muscles, terminate in one of several different types of low threshold mechanoreceptor organs that are highly sensitive to physical stimulation of the skin. Human skin is categorized as either hairy or glabrous (non-hairy) skin, based on the presence or absence of hair. Different populations of cutaneous receptors are found in the hairy and glabrous skin. For example, Pacinian, Merkel, Ruffini and various types of hair receptors are found within hairy skin, whereas glabrous skin contains Pacinian, Merkel, Ruffini and Meissner receptors (Vallbo, Olausson, Wessberg, & Kakuda, 1995). The skin at the pad of the fingertip is glabrous skin and therefore, the cutaneous receptors most likely contributing to the light touch effects on balance control are those associated with glabrous skin. For this reason, the subsequent discussion will focus on these receptors.

Cutaneous mechanoreceptors in the glabrous skin respond to physical (mechanical) deformation of the skin and transduce the deformation into electrical impulses to traverse and be interpreted by the CNS. Each receptor type conveys specific features from a physical stimulus, responding differentially, providing the CNS with distinct information about the features of the object touched. Although cutaneous mechanoreceptors can respond to a wide range of stimuli, each has a specific modality which they are most sensitive to. Charles Sherrington dubbed the term *adequate stimulus* – meaning, the stimulus for which a receptor shows the greatest responsiveness (Sherrington, 1906). Meissner corpuscles are most responsive to slips of the finger or flutter, Merkel disk receptors are highly responsive to texture or the size and shape of objects, Pacinian corpuscles respond best to high frequency vibration (greater than 300Hz), and Ruffini endings are predominantly activated by skin stretch, with directional sensitivity (Knibestöl, 1973, 1975). The nature of these adequate stimuli are partly attributed to psychophysical studies where individual afferents were identified using microneurography and then electrically stimulated through the same electrodes while participants reported sensations (Vallbo et al. 1984). Interestingly, Ruffini afferents did not elicit any sensations upon electrical stimulation, lending to arguments that Ruffini endings play a larger role in proprioception than tactile discrimination (Edin, 2001; Edin & Johansson, 1995).

Single Cutaneous Mechanoreceptor Afferent Classification

When investigating single cutaneous mechanoreceptors using microneurography, it is the activity of the single afferent's axon that is recorded, also referred to as an afferent unit. Therefore, identification of the mechanoreceptor specifically being investigated is indirectly inferred from the pattern of activity in the isolated afferent unit. To do so, physical stimuli are applied to the end organelle's receptive field and the pattern of activity, or action potentials, is recorded in the associated afferent unit. The adequate stimulus of each receptor, along with other responses to various physical stimuli, are used to categorize the cutaneous mechanoreceptor into different afferent types. Cutaneous afferents in the glabrous skin are categorized as either fast adapting or slow adapting, based on the afferent's response to a dynamic and static stimuli. Fast adapting afferents respond with a burst of impulses during the application and removal of stimuli, likely by bending the axon terminal within the capsule generating a receptor potential (Takahashi-Iwanaga & Shimoda, 2003). In contrast, slow adapting afferents respond with a sustained discharge to a static stimulus (Johansson & Vallbo, 1983). Subsequently, fast and slow adapting afferents are further subcategorized as either type I or II; determined by 1) the receptive field size, 2) the number of hot spots (areas of high sensitivity to mechanical stimulation), and 3) the firing pattern to a slowly applied stimulus. Type I units have small well-defined receptive fields, likely due to being more superficially located at the junction between the dermis and epidermis. In addition, type I units have multiple hot spots, likely due to several end organ receptors per afferent unit. Type I units also show a higher firing frequency to the dynamic phase of a slowly applied linear stimulus. In contrast, type II units have wider receptive fields with obscure boarders and a single hot spot, likely due to being located deeper within the dermis (Johansson & Vallbo, 1983). Using these criteria, recorded afferents are classified as one of four specific types: fast adapting type I (FAI), presumed to terminate with a Meissner corpuscle (Jänig, 1971); fast adapting type II (FAII), presumed to terminate with a Pacinian corpuscle (Lindblom & Lund, 1966); slow adapting type I (SAI), presumed to terminate with a Merkel disc receptor; and slow adapting type II (SAII), presumed to terminate with a Ruffini ending (Chambers, Andres, von Duering, & Iggo, 1972; Iggo & Muir, 1969). It is not always possible to disambiguate the afferent type of a recorded unit. In these instances, the convention in the field is to categorize the unit as being ectopic. Given the rich density of highly sensitive cutaneous mechanoreceptors in the glabrous skin of the fingertip and the adequate stimuli related to these receptors, it is logical to expect that cutaneous mechanoreceptors are responsive to the light touch contact used during balance stabilization. Microneurography will allow for the identification of which specific types of receptors might contribute functionally to the control of balance.

Stimulation at the Fingertip During Light Touch While Standing

When light touch at the fingertip is used to assist with balance stabilization the most logical receptors to signal the interaction of the fingertip with the touch reference are those located in the pad of the fingertip. Previously, it was demonstrated that type I receptors, with their smaller, more well-defined receptive fields, constitute about 70% of the total tactile innervation of the glabrous skin of the hand (Johansson & Vallbo, 1983). Moreover, Meissner corpuscles are preferentially located on the sides of the papillary ridges (Bolanowski & Pawson, 2003), which presumably facilitates the responsiveness of these receptors to slips across the finger (Johansson & Westling, 1987). In addition, Meissner corpuscles are differentially activated by tangential forces in the proximal and radial directions (Birznieks, Jenmalm, Goodwin, & Johansson, 2001), suggesting direction-specific sensitivity. It is therefore reasonable to expect that Meissner corpuscles, in particular, are well suited to provide important sensory cues from the fingertip related to balance control.

Other cutaneous receptors are also likely to contribute to the sensory benefit of light touch to balance control. For example, the other type I receptors, Merkel receptors, which also have a high density in the glabrous skin, are preferentially located at the apex of the papillary ridges (Quilliam, 1978). This arrangement makes the Merkel receptors adept at signaling sequential changes in contact points between the skin and the touched surface, which thus signals motion across the skin (Olausson, Wessberg, & Kakuda, 2000). Indeed, Merkel receptors show a bias in firing to tangential forces in the distal direction, contrasting Meissner corpuscles. Ruffini endings, activated by skin stretch, are also likely to be activated by sway-induced shear forces at the fingertip stretching the skin (Hulliger et al., 1979; Knibestöl, 1975) and have also demonstrated a directional bias with preferred activation to tangential forces in the proximal direction (Birznieks et al., 2001). Cutaneous receptors with their receptive fields located outside of the pad of the fingertip could also contribute to the sensory benefit of light touch to balance control. In particular, type II receptors have large receptive fields that can be activated by skin deformation that occurs at more distant locations. For example, Pacinian corpuscles distant from the contact points were shown to become activated during precision grip tasks (Westling & Johansson, 1987). Taken together, each of the classes of cutaneous mechanoreceptors could offer light touch-related sensory feedback relevant to the control of balance.

Precision grip experiments have shown that cutaneous sensibility is necessary in sensorimotor connections used to tune grip force between the thumb and index finger (Johansson and Westling 1984; Westling and Johansson 1984). On an individual receptor basis, certain tactile units were found to be more sensitive than others during specific events within the precision grip lift task (Westling & Johansson, 1987). For example, type I units showed a marked initial response when the pinch grip force and load force were changing. This might suggest that when using light touch to aid in balance control type I units could play a role signaling the onset of sway-related motion or changes in direction of sway by preferentially being active with a change in vertical or shear force. Precision grip experiments also demonstrated that FAII units were highly responsive to friction in relation to movement of the gripped object (Westling & Johansson, 1987). Therefore, FAII units might be well suited to detect the onset or offset of relative motion between the finger and contact reference when light touch is being used for stabilizing balance. From this work, it is apparent that individual cutaneous receptors code specific events during precision grip tasks. If similar receptor specificities emerge when light touch is used to stabilize balance, it might explain the direction-specific behavioral reactions seen by Misiaszek et al. (2016) and suggest that the hands, with their rich cutaneous sensory innervation, are uniquely equipped to provide important sensory feedback for balance control when the hands are engaged with objects in the environment.

In addition to the cutaneous mechanoreceptors of the glabrous skin, lightly touching a reference for balance stabilization could stimulate receptors in the hairy skin or other non-cutaneous somatosensory receptors. That is, the friction between the fingertip and the contact surface could result in changes in joint angles of the index finger, which could become more pronounced or apparent when large displacements occur, such as during the touch-displacement studies of Misiaszek and colleagues (Misiaszek et al. 2016). This change in finger joint angles could then activate receptors sensitive to stretch of the skin across the joint (Collins & Prochazka, 1996; Hulliger et al., 1979), stretch of muscles whose tendons cross the joints (Akazawa, Milner, & Stein, 1983), or intra-articular joint receptors (Ferrell, Gandevia, & McCloskey, 1987). Moreover, the slip of the contact across the fingertip likely causes vibration that could be detected by vibration sensitive receptors, such as fast adapting cutaneous afferents (Talbot, Darian-Smith, Kornhuber, & Mountcastle, 1968), or muscle spindles, in the finger or at more distant points. Therefore, multiple receptor types have the potential to contribute sensory feedback that could be integrated in light touch-related balance influences. This thesis will not address all of the possible sensory inputs but focuses on delineating the potential role of cutaneous mechanoreceptors in the glabrous skin of the fingertip in the light touch-related stabilization of balance.

Materials and Methods

Participants

A total of 24 volunteers (age 19 – 65) participated in this study which consisted of 55 experimental sessions. All participants provided written informed consent in a protocol approved by the University of Alberta Health Research Ethics Board (Pro00072682), in accordance with the Declaration of Helsinki. None of the participants reported any neuromuscular, neurologic or metabolic health concerns.

This study was performed in two parts. In the first, we determined if activation of single cutaneous afferents of the hand influenced the excitability of motoneuron pools of ankle muscles. In the second, we investigated the responses of individual cutaneous afferents innervating the hand by the median nerve to rapid displacement of a light touch reference across the receptive field of the afferent, as well as the pad of the index finger.

Part 1: Single Cutaneous Afferent Interlimb Connectivity

Participants and Set-up

A total of 18 participants (10 male, 8 female) were tested in 42 experimental sessions. Microneurographic recordings of single afferents of either the left of right median nerve at the wrist were obtained. To do so, participants were seated comfortably in a reclined chair that provided full support of their body, including the head

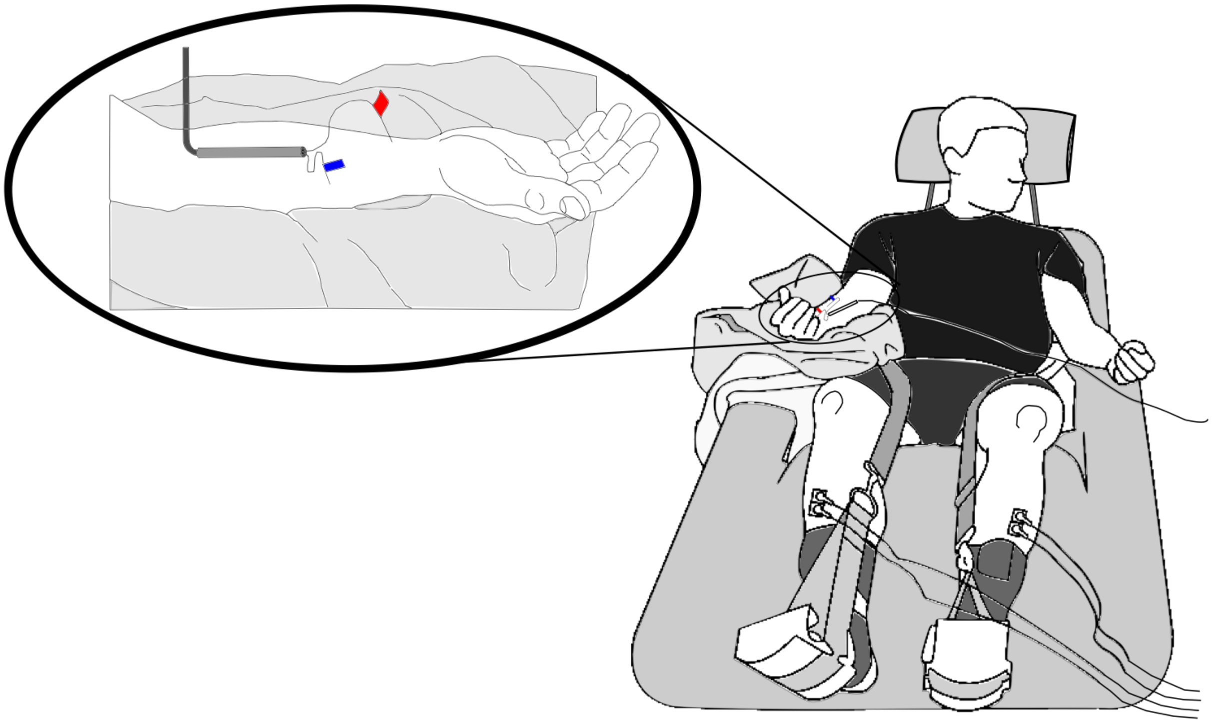


Figure 1 | Experimental setup and microneurography electrode placement. Participants were seated comfortably, arm secured in a vacuum form pillow, splinted about the ankle joint, and EMG was recorded from the left and right tibialis anterior and soleus. In the expanded image in the top left: Red flag is the active electrode; blue flag is the reference electrode. The active electrode was inserted percutaneously into the median nerve. The reference electrode was placed approximately 5 cm proximal, and slightly lateral, relative to the active electrode. Both electrodes were connected to a headstage unit secured to the forearm.

and limbs (Fig. 1). The arm that was used for the microneurographic recording was placed in a comfortable, relaxed, and supinated position supported by the chair. The forearm and wrist were then stabilized in position with the use of a vacuum form pillow to encourage the participant to fully relax their arm and minimize any unwanted movement. The feet were placed into splints that minimized ankle joint motion to facilitate isometric contraction of the muscles at the ankle.

Microneurography

The location of the median nerve at the wrist was identified by using a handheld stimulator, applying transcutaneous electrical stimulation at approximately 2 Hz with a pen-like probe. Using participant feedback, the probe was moved across the wrist to identify the location of strongest perceived sensation radiating into the innervation territory of the median nerve at the lowest stimulus strength. The skin overlying the identified region was then cleaned with a 70% isopropyl alcohol solution. The specific insertion point was then selected to avoid tendons and blood vessels. Typically, the site selected was approximately 2 cm proximal to the wrist crease, between the tendons of palmaris longus and flexor pollicis longus. An uninsulated reference electrode was inserted approximately 5 cm proximal and slightly lateral to the active electrode. The two electrodes were then connected to an isolated head stage (Neuro Amp EX headstage, AD Instruments, Sydney, Australia) secured to the volar aspect of the participant’s forearm (Fig. 1). The signal was then amplified by the head stage (Neuro Amp EX headstage, AD Instruments, Sydney, Australia) at a gain of 100, displayed to an oscilloscope (Tektronix TDS 3014B, Tektronix Inc., Beaverton, OR, USA), and transmitted to a loudspeaker and headphones to facilitate the identification of single afferents. To reduce electrical noise, the experimenter was grounded to the participant by connecting a disposable Ag/AgCl surface electrode on the dorsal surface of the experimenter's hand, to a surface electrode on the volar surface of the participant's forearm.

After site selection and the percutaneous insertion of the needle electrodes, the active electrode was advanced by hand until the median nerve was penetrated. Penetration of the nerve is best indicated by sudden paresthesia and sometimes distinct injury bursts, of short duration, in the neural recording (Vallbo & Hagbarth, 1968). Once the nerve was penetrated, the active electrode was slowly advanced until single cutaneous unit activity was recorded. Single unit classification was done online, with visual and auditory feedback from physically applied stimuli (see Fig. 2). Afferents of glabrous skin were classified as Fast Adapting type I and II (FAI and FAII), and Slow Adapting type I and II (SAI and SAII) following previously establish criteria (Johansson & Vallbo, 1983; Knibestöl, 1973, 1975). Slow adapting receptors respond with a sustained discharge to a physical stimulus, whereas fast adapting receptors respond transiently upon application and removal of stimulus. Type I afferents have small well-defined receptive fields, with multiple hot spots, and type II afferents have wider receptive fields with obscure boarders, and single hot spots. Determining the type of afferent discharge (continuous or discrete), receptive field size, and threshold, was done using calibrated

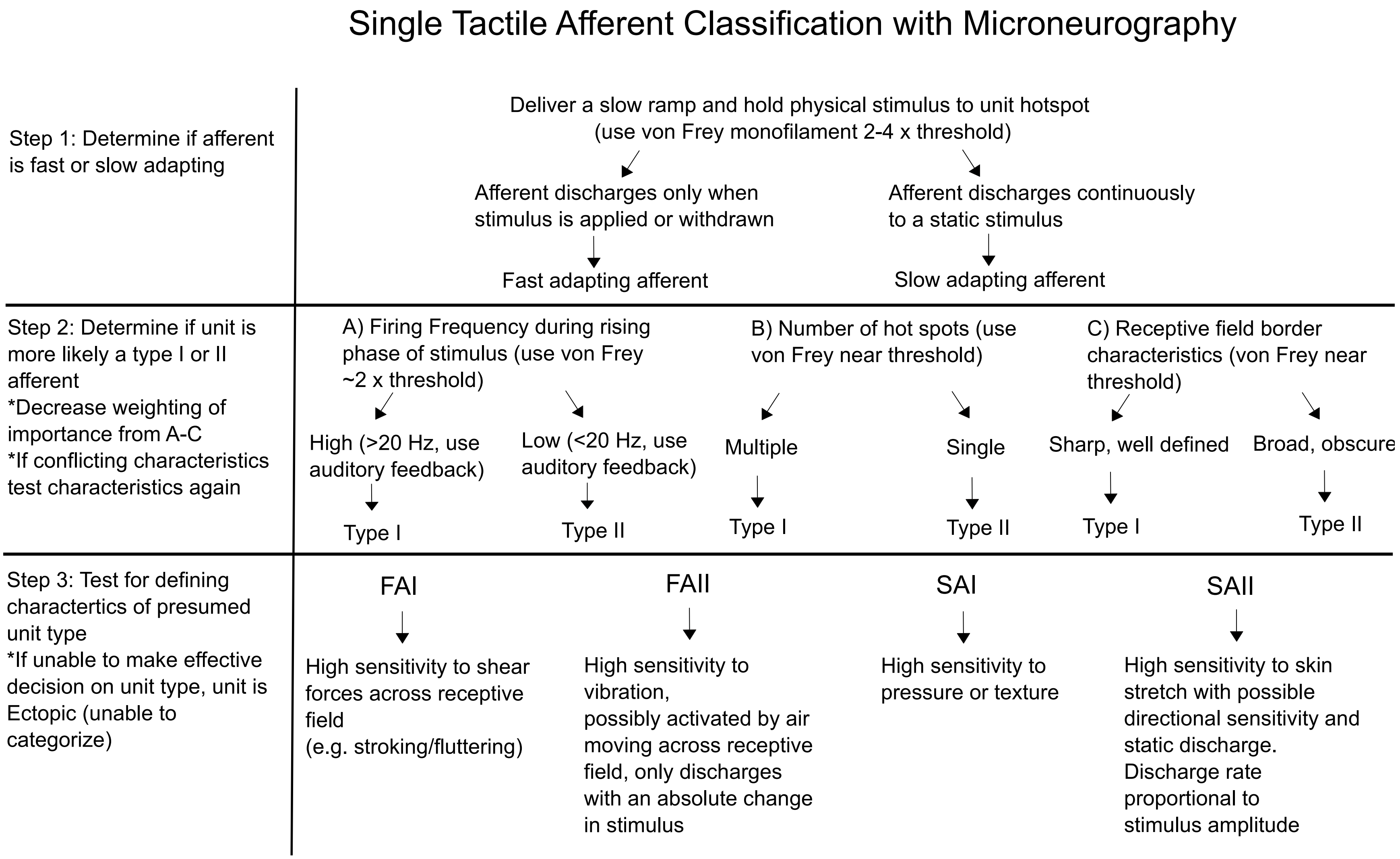


Figure 2 | Single tactile afferent classification schema.

von Frey monofilaments (Semmes-Weinstein Monofilaments, North Coast, San Jose, CA, USA). If an afferent was unable to be classified, it was considered to be ectopic. A maximum cumulative search time of 45 minutes was permitted for each experimental session, which might include multiple electrode insertions.

Electromyography

EMG activity was recorded with pairs of Ag/AgCl disposable surface electrodes (NeuroPlus A10040, Vermed, Bellows Falls, Vermont, USA) placed over the left and right TA and SOL muscles in a bipolar configuration. Electrodes were positioned according to the SENIAM (Surface EMG for Non-Invasive Assessment of Muscles) guidelines (Hermens et al., 1999). Consequently, electrode placement for TA was 1/3 the distance from the caput fibulae to the medial malleolus, and SOL electrode placement was 2/3 the distance between the medial condyle of the femur to the medial malleolus. A single ground electrode was placed over the medial surface of either the right or left tibia. Prior to electrode placement, the skin was shaved and cleaned with a 70% isopropyl alcohol solution. Impedance was measured with an impedance meter (BI-sim impedance meter, Brundinnovation HB, Umeå, Sweden) to ensure an impedance of less than 10 kΩ, at 20 Hz. In some instances, the skin was abraded with sandpaper and cleaned again if the initial preparation resulted in a high impedance.

Protocol

Upon locating, isolating and characterizing a single mechanoreceptive afferent (as described in *Microneurography*) the unit was activated by tactile stimuli applied manually to the hot spot by the experimenter, while the participant maintained isometric activation of target muscles. Tactile stimulation of the unit was achieved by either a) pressing a von Frey monofilament with an applied force of ≥ 4x the receptor threshold, or b) indenting the skin with a stiff blunt tipped probe (surface area approximately 2.4 mm^2), typically used for units with a threshold ≥0.6g. For SA units, the tactile stimulus was persistently applied. If the unit showed signs fatigue, such as firing frequency dropping below 1 Hz, the stimulus was withdrawn for 1-3 seconds before reapplying. For FA units, the tactile stimulus consisted of low frequency taps, for durations <2 seconds, at varying rhythmicity to minimize the risk of entrainment of the unit's firing pattern. Bilateral isometric contraction of either TA or SOL was achieved by dorsiflexing or plantarflexing against the resistance provided by the splints. Participants were asked to contract at 50% of their maximum voluntary contraction (MVC), which had been established prior to insertion of the microneurographic needle electrodes. Participants were provided with visual feedback of the root mean square (RMS) of the EMG signal of the target muscle, ipsilateral to the median nerve being recorded, to assist with maintaining a consistent level of background activity. Background contractions were sustained in bouts of 1 to 2 minutes of duration, with 2 to 3 minutes of rest between bouts, to ensure sufficient quantity of data, while minimizing participant fatigue. Recordings in each muscle were performed in blocks, and in all experiments TA data was collected before SOL data. Data were only included in the subsequent analysis if recordings for both TA and SOL were achieved for that afferent unit.

Data Acquisition

Data were recorded to a computer for later analysis with a 16 bit, 16-channel data acquisition system (PowerLab 16/30, AD Instruments, Sydney, Australia) using LabChart Pro 8 software (LabChart Pro 8, AD Instruments, Sydney, Australia). The microneurographic signal was initially preamplified at a gain of 100 and high pass filtered at 10 Hz with an isolated headstage (Neuro Amp EX headstage, AD Instruments, Sydney, Australia). The signal was subsequently band-pass filtered at 300–2000 Hz, passed through a noise eliminator (Hum Bug, Quest Scientific, Vancouver, British Columbia, Canada), and sampled at 20 kHz. EMG data were band-pass filtered at 2-1000 Hz (g.BS amp Biosignal Amplifier, g.tec medical engineering GmbH, Schiedlberg, Sierningstrasse, Austria) and sampled at 2 kHz.

Analysis

Coupling of neuronal activity between the afferents recorded in the median nerve and the TA and SOL motoneuron pools was determined by identifying changes in EMG amplitude correlated to the presence of a spike in the recorded afferent using the STA technique (Baker & Lemon, 1998). To do so, individual spikes within the single unit microneurographic activity were discriminated offline (Fig. 3) using Spike2 template

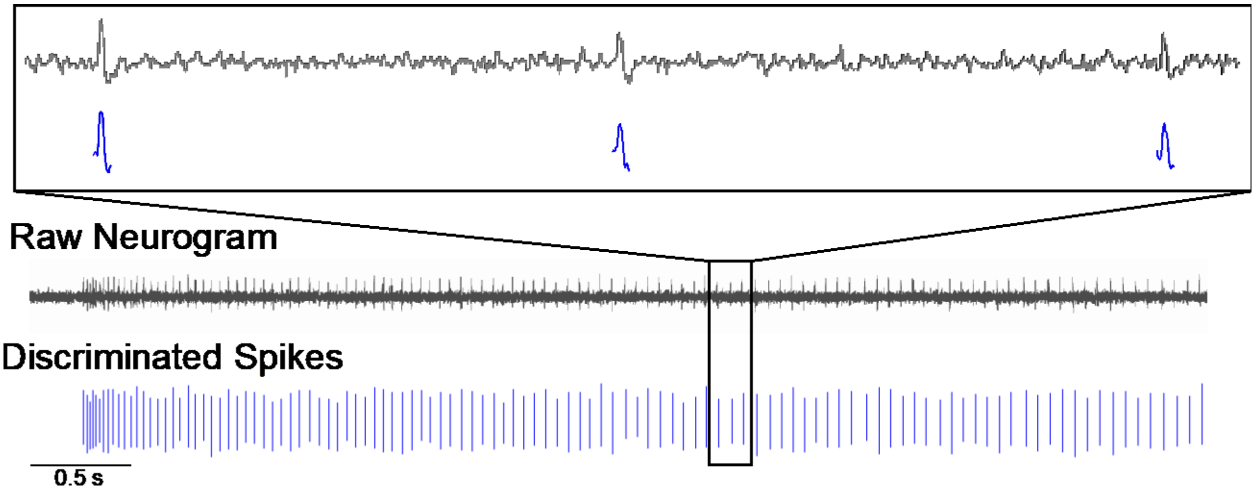


Figure 3 | Illustration of spike discrimination from the raw neurogram recording. Raw neurogram is the train of spikes recorded using microneurography and imported into Spike2. Individual spikes were discriminated offline using Spike2 template matching software and subsequently visually inspected. Afferent discriminated was a slow adapting type I unit.

matching software (Spike2 version 6.18, Cambridge Electronic Design, Milton, Cambridge, England). After template matching, the individual spikes were visually inspected to ensure only a single unit had been identified throughout the recording. Subsequently, for each identified afferent spike a 250 ms segment of the target EMG data trace (RMS of the signal with a 5 ms window) was extracted and averaged, aligned to the onset of the cutaneous afferent spike discharge. Each trace included a 50 ms pre-spike period. A 99% confidence interval was calculated about the average for the initial 90 ms of the trace, which included the 50 ms pre-spike interval and the initial 40 ms post-spike.

Evidence of synaptic coupling was considered to be present when the STA trace exceeded the 99% confidence interval continuously for ≥2.5 ms, calculated using a custom-written MatLab script (MATLAB R2016b, The Mathworks, Natick, MA, USA). For a mechanoreceptive afferent to be considered as demonstrating connectivity to a muscle of the lower limb, only one of the four muscles recorded (left and right TA and SOL) needed to meet the criteria for showing connectivity. The latency of synaptic coupling was calculated from the time of afferent spike onset to the time when the STA trace first exceeded the confidence band. The amount of signal excursion beyond the confidence band was not quantified and therefore, only absolute responses were reported, i.e. descriptive classifications that the confidence band was surpassed in either the positive or negative direction was used. Positive deflections in the STA trace represent net excitatory responses, whereas negative deflections represent net inhibitory responses. In the event that the averaged RMS EMG signal exceeded the confidence band more than once, only the first response was reported. Responses were categorized into three latency epochs, early (40 – 80ms), middle (80 – 120 ms), and late (>120 ms), similar to previous interlimb cutaneous reflex studies (Zehr et al., 2001). Only units that demonstrated responses at early or middle epochs were included in the descriptive analysis. Responses were categorized based on the location of the afferent in the hand and the latency of the response. As well, all early and middle latency responses were reported, categorized based on the type of afferent recorded, the latency of response demonstrated, and the muscle in which the response was seen.

Part 2: Single Afferent Response to Rapid Light Touch Displacements

Participants and Set-up

A total of 9 participants (2 male, 7 female) were tested in 13 experimental sessions. Microneurographic recordings of single afferents of either the left of right median nerve at the wrist were collected while applying a light touch displacement. For this, the same experimental set-up was used as described in Part one, with two differences: 1) EMG data were not collected and therefore no ankle splints were used, and 2) to facilitate positioning the touch device over the hot spots of identified afferents, elastic bands were secured around the distal interphalangeal joints of the second, third, and fourth digits, connected to a stiff board placed under the participant's hand.

Touch Device

Displacement of the light touch contact surface across the skin, over the hot spot of the receptor or the pad of the index finger was achieved by the use of a 3D printed touch surface, driven by a stepper motor (NEMA-23 57STH56-2804MB; Dongzheng Motor Co. LTD; China) (Fig. 4A). The touch contact area of the device was 3.5 cm long x 1.5 cm wide. A load cell (Micro Load Cell 0-5 kg CZL635; Phidgets Inc., Calgary, Alberta, Canada) was integrated in the apparatus to measure the vertical force applied during touch, while a linear potentiometer (Penny & Giles SLS095; Christchurch, Dorset, UK) measured the linear displacement of the contact surface. The touch device was mounted to a microscope arm that allowed for the control of pitch, yaw, and roll position of the device to ensure the contact surface was appropriately applied to the skin over the receptor hot spot or the pad of the index finger without disturbing the microneurography set-up. The device was shielded with a metal mesh to reduce electrical noise in the recordings.

Protocol

After a mechanoreceptive afferent was identified and characterized (as described in *Microneurography*), the touch surface was carefully lowered and centered over the hot spot of the identified unit. Twenty alternating rapid displacements (1.25 cm, 120 ms duration) ten away from the participant and ten towards the participant were initiated by an experimenter, with a 1-3 s break given between each displacement (Fig. 4B).

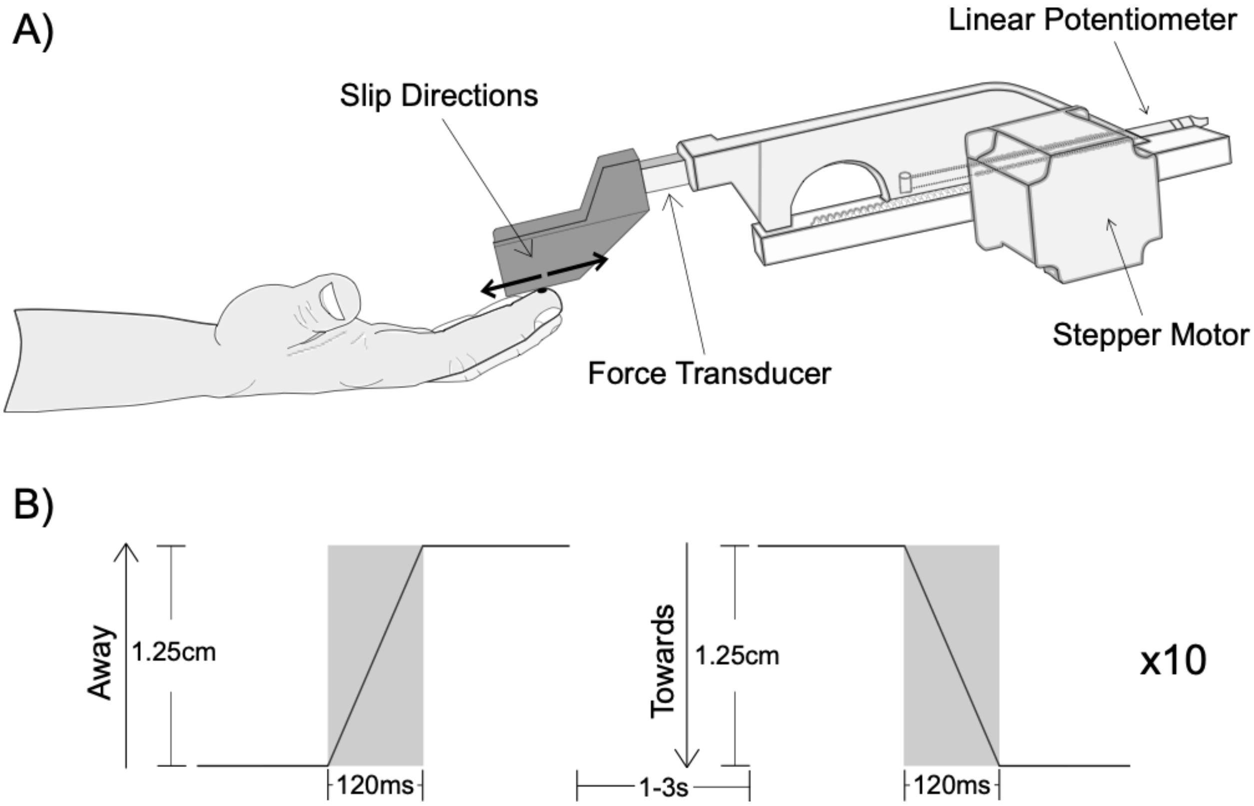


Figure 4 | Experimental setup for experiment two, characterizing afferent discharge to a rapid light touch displacement over its hot spot. A) The touch surface was positioned over the afferent's hot spot in the pad of the index finger (black dot) with less than one newton of force. B) Twenty rapid displacements total, ten away from and ten towards the participant were delivered, with 1-3 seconds between each displacement.

Following this, the touch surface was positioned over the pad of the index finger and a successive twenty alternating rapid displacements, ten in each direction, were delivered. The load applied to the finger was monitored throughout to ensure it remained ≤1 N.

Data Acquisition

Data were recorded and stored as in Part one, with the exception that no EMG was recorded and the microneurographic signal was sampled at 100 kHz. The linear position of the touch device was low pass filtered at 1 kHz and sampled at 2 kHz, and touch force was low pass filtered at 20 Hz and sampled at 2 kHz.

Analysis

Afferent spike activity was discriminated using the same process as described for Part one. Following the spike discrimination, raster plots of the activity of an individual afferent were created displaying the activity from all ten touch displacements of the same direction, along with the touch device position and touch force, for a 350 ms duration, which included a 150 ms period prior to the onset of the touch displacement. The spikes within the ten raster plots were then converted into a peri-event time histogram, utilizing 30 ms bins. In addition, firing frequencies of each unit over the 350 ms analysis period were estimated using 10 ms bins to calculate the instantaneous firing frequency. The firing frequencies were then averaged for each unit type and for each direction of displacement, across all the recorded units. Custom-written MatLab (MATLAB R2016b, The Mathworks, Natick, MA, USA) scripts were used in the analysis.

Results

Part 1: Single Cutaneous Afferent Interlimb Connectivity

Part one investigated potential interlimb connections between single cutaneous mechanoreceptors of the hand innervated by the median nerve, and muscles of the lower limb. Across 42 experimental sessions, a total of 42 afferents serving cutaneous mechanoreceptors were recorded from the median nerve at the wrist, with simultaneous EMG data collected from both the ipsilateral and contralateral TA and SOL (iTA, iSOL, cTA, cSOL), relative to the site that microneurography was performed on, and was therefore included in subsequent analysis. Of the 42 experimental sessions, there was no data collected in 14 experiments due to either an inability to penetrate the nerve with the electrode or a change in electrode characteristics such that a sufficiently high signal to noise ratio could not be maintained. Of the 42 cutaneous afferents recorded, 15 were FAI units, 5 were FAII units, 13 were SAI units, 6 were SAII units, and 3 were ectopic units.

An example trace of STA EMG activity from the cSOL of one participant is depicted in Figure 5. This trace was derived from the average of 971 discharges of a SAI unit and demonstrates a clear positive response with an onset latency of 41.0 ms, as indicated by the vertical dashed red line. Figure 6 depicts additional STA traces illustrating that both early and middle latency responses were observed in muscles of the ankle, related to afferent activity in the median nerve of all cutaneous mechanoreceptor types identified.

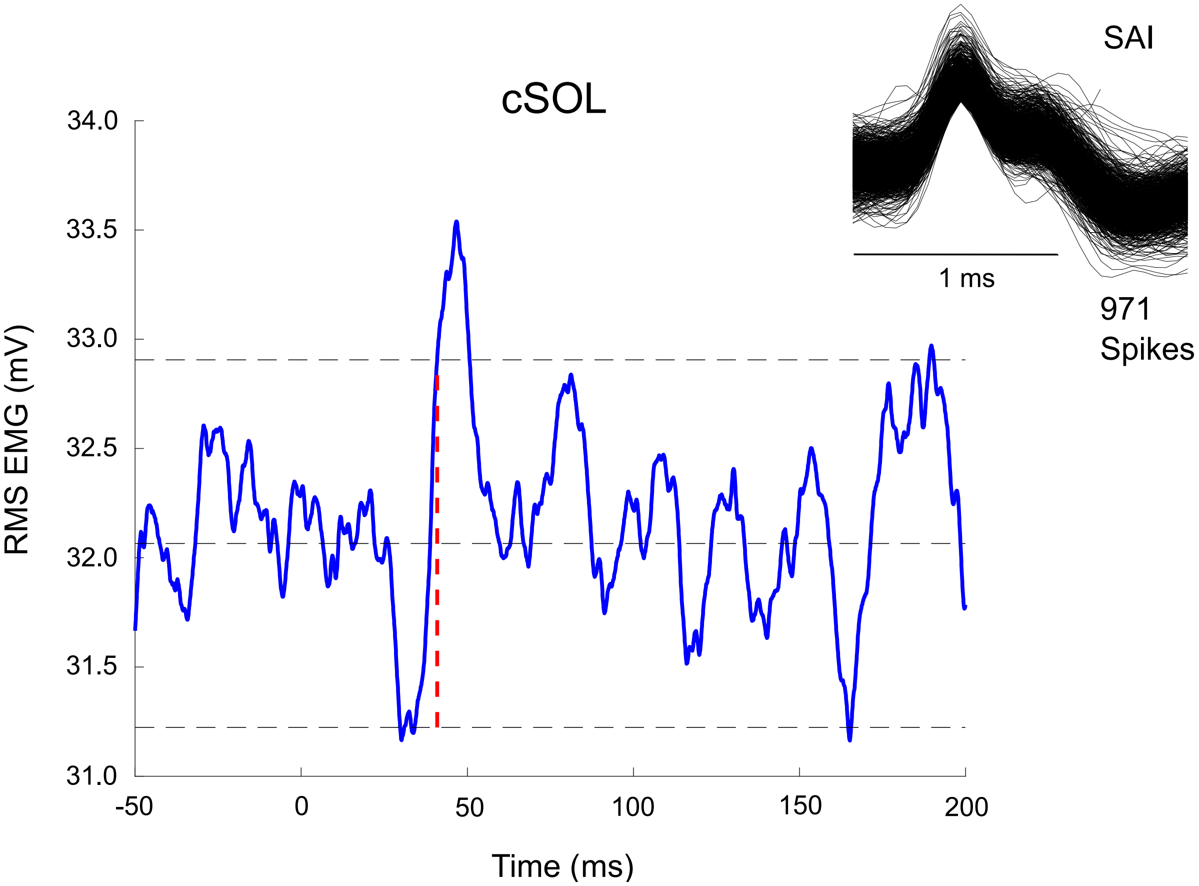


Figure 5 | Example of a spike triggered averaged EMG trace. The blue line represents the averaged RMS EMG trace from cSOL obtained from 971 traces triggered by spikes recorded in a single SAI afferent. The horizontal dashed black lines represent the boundaries of 99% confidence interval, along with the mean of the ongoing background activity. The vertical dashed red line indicates the onset of the first significant response. The inset depicts an overlay of all 971 discriminated spikes used to trigger the EMG averaging.

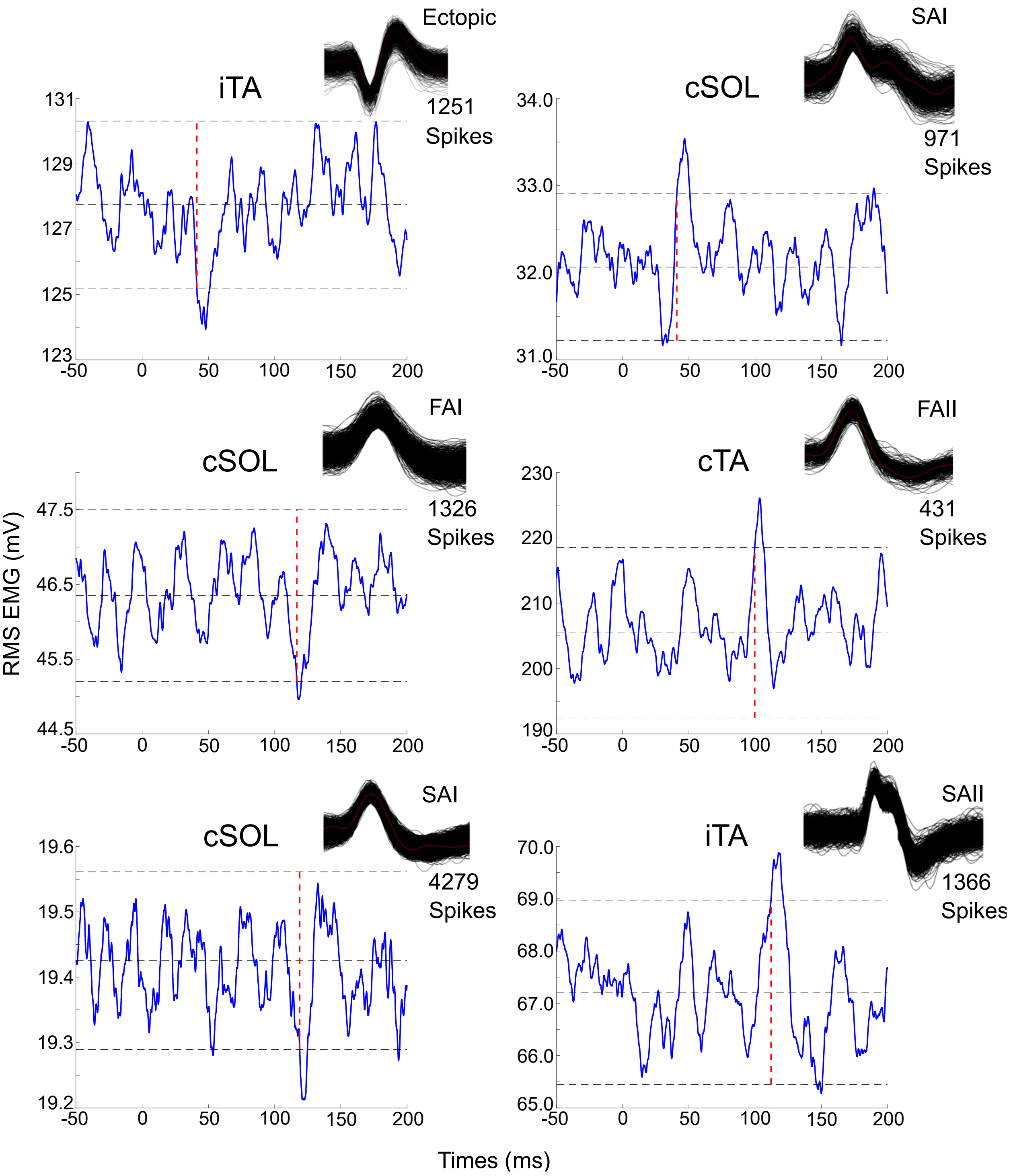


Figure 6 | Various examples of the different types of connectivity seen. Connections were demonstrated at varying latencies, in the positive and negative direction, in various muscles, from all afferent types, and generated from a wide range of spike triggered averages used in each.

Of the 42 mechanoreceptor afferents recorded in the median nerve, 34 (81%) produced a demonstrable response in the STA EMG trace of at least one muscle within the early or middle latency periods, with 12/15 (80%) FAI, 5/5 (100%) FAII, 11/13 (85%) SAI, 4/6 (67%) SAII, and 2/3 (67%) ectopic units producing responses in at least one muscle. In addition, 18 of the 42 units (8 FAI, 4 FAII, 5 SAI, and 1 ectopic) produced demonstrable responses in the STA EMG traces of more than one muscle. Table 1 summarizes the appearance of responses in the STA EMG traces across all 42 recorded afferents, listed as the latency of the earliest response, in ms, with the sign of the response in brackets.

Mechanoreceptors that were associated with early and middle latency responses in the STA EMG traces of the ankle muscles were distributed throughout the sensory territory of the median nerve. As shown in Figure 7, mechanoreceptors in the volar surface of the fingers, including pads, as well as broadly throughout the volar surface of the hand were identified with significant responses in the EMG of the ankle muscles. In addition, the few afferents related to receptors on the dorsum of the hand also resulted in modulation of STA EMG traces. Figure 8 further separates the results according to the muscle in which a response was observed and by response latency. This demonstrates, along with the data in Table 1, a bias in the observed responses towards early latency responses in TA.

Table 1 | All instances of Interlimb responses observed. Responses are reported relative to the muscle the response was observed in, and the latency of the response in ms. (+) and (-) symbols indicate whether the response was excitatory or inhibitory respectively.

	Early Latency					Middle Latency			
	Contralateral		Ipsilateral			Contralateral		Ipsilateral	
	SOL	TA	SOL	TA		SOL	TA	SOL	TA
FAI	40.0 (-)	44.7 (-)	58.3 (+)	44.0 (+)	FAI	90.4 (-)	92.1 (-)		85.1 (+)
	49.9 (+)	75.6 (-)		51.4 (-)		95.2 (-)	98.8 (+)		
	56.8 (+)	77.4 (-)		58.1 (-)		102.5 (-)	98.8 (-)		
				58.8 (+)		116.8 (-)	109.3 (+)		
				61.4 (-)					
				62.3 (+)					
				73.1 (-)					
FAII	75.9 (-)		46.0 (-)	40.3 (+)	FAII		99.7 (+)		
			68.7 (-)	50.6 (+)			117.5 (+)		
			69.0 (+)	54.3 (+)					
				65.4 (+)					
SAI	41.0 (+)	45.6 (-)	40.0 (+)	57.1 (+)	SAI	87.3 (+)	80.1 (-)	91.7 (-)	119.8 (+)
	51.7 (+)	57.8 (+)		58.2 (+)		99.9 (+)	84.7 (+)		
	80.0 (-)	67.5 (-)		64.2 (+)		111.3 (+)			
		72.1 (-)				119.0 (-)			
SAII		58.8 (+)			SAII	86.3 (+)		103.6 (-)	112.0 (+)

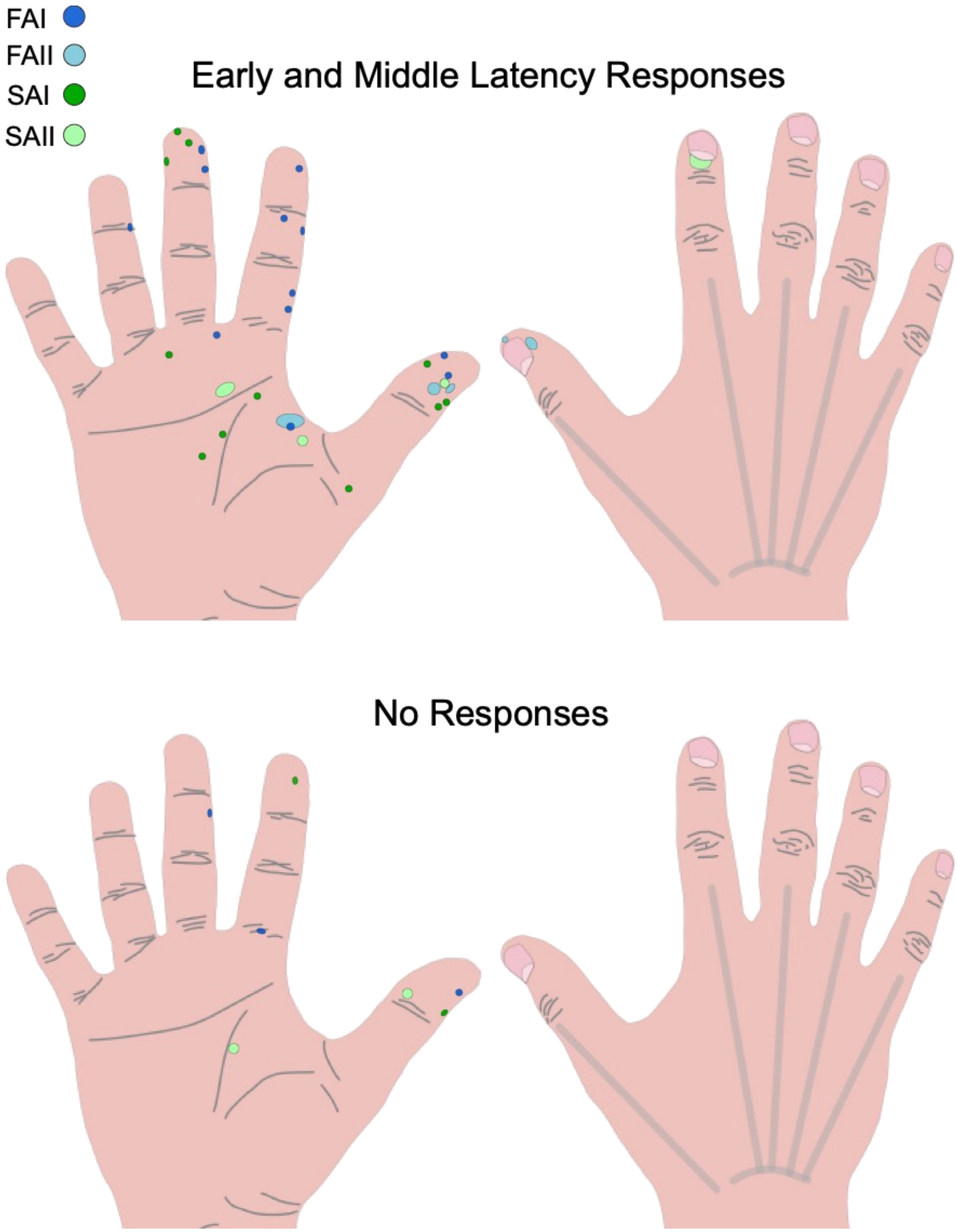
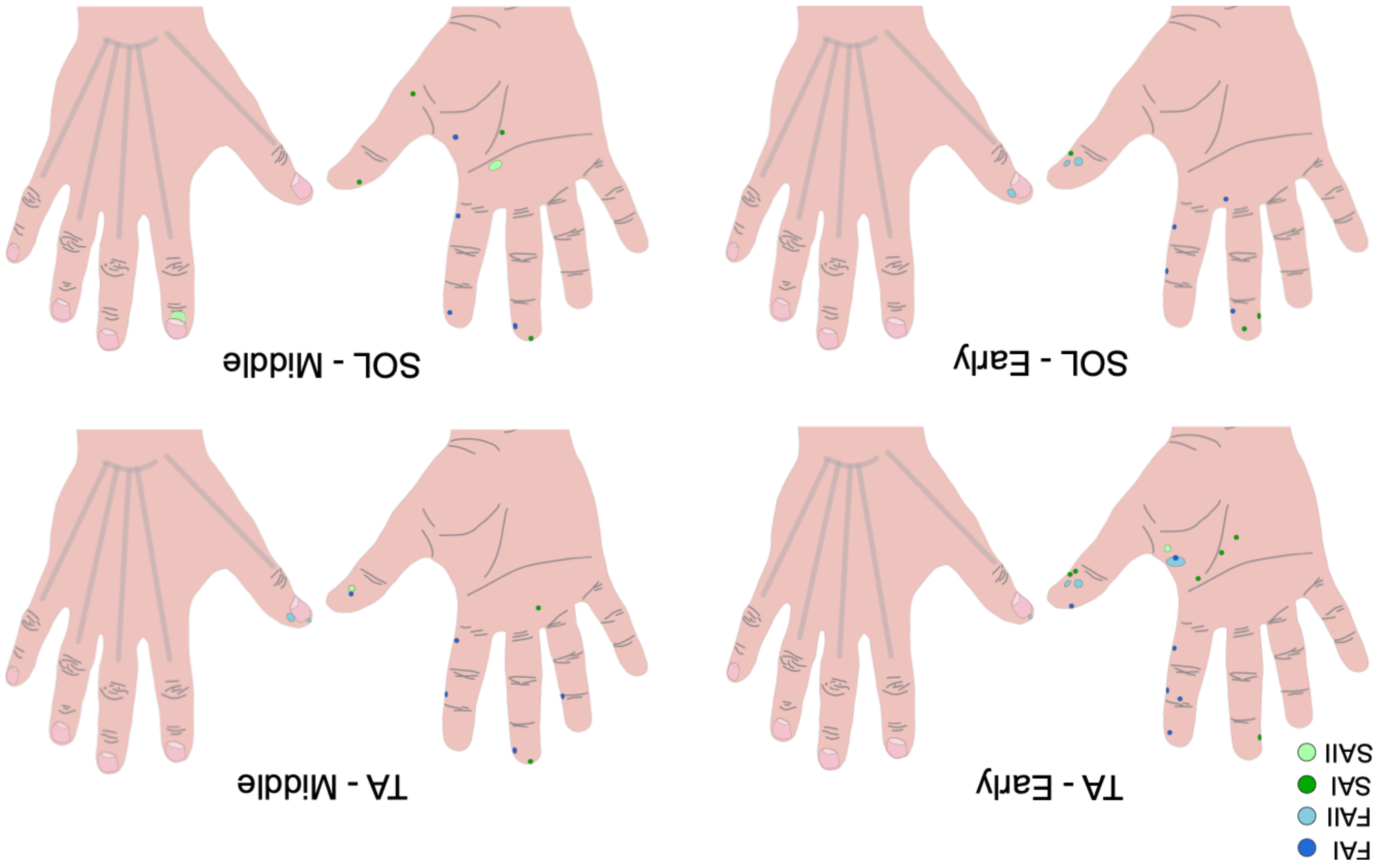


Figure 7 | Type and distribution of mechanoreceptive afferent hot spots recorded in experiment one. Data were collected from both the left and right median nerve but collapsed into a single image for illustrative purposes. Units that demonstrated responses in the STA EMG traces of the ankle muscles at early and middle latencies are shown in the upper image. Units that did not produce responses are shown in the lower image. Ectopic units not shown.

Figure 8 | Distribution of afferent types relative to the muscle and latency in which responses were seen after STA.



Part 2: Single Afferent Response to Rapid Light Touch Displacements

Part two investigated the firing characteristics of single cutaneous mechanoreceptors innervated by the median nerve in response to rapid displacements of a light touch contact across their receptive field. A total of 12 afferents serving cutaneous mechanoreceptors were recorded from the median nerve at the wrist. One SAII unit recorded was not included in the analysis because the contact surface of the touch device could not be positioned over the unit's receptive field, which was located in the nail bed of the second digit. Therefore 11 afferent units were included in the analysis comprised of: 3 FAI units, 2 FAII units, and 6 SAI units. Figure 9 shows the type and distribution of all the cutaneous afferents collected. Ten of the receptors were located on the volar surface of the distal phalanxes of digits II through IV.

Afferent Activity in Response to Rapid Displacements of a Light Touch Contact

Rapid displacement of a light touch surface in contact with the hot spot for a receptor invariably resulted in changes to the ongoing activation of the recorded afferents, regardless of the type of mechanoreceptor served. Figures 10 through 12 depict representative examples of the afferent activity recorded from individual FAI, FAII, and SAI afferents in response to light touch displacements in both directions. The third panel from the top, of each set of four panels, depicts hashes representing the discriminated afferent spikes. Each row of discriminated spikes represents one trial of

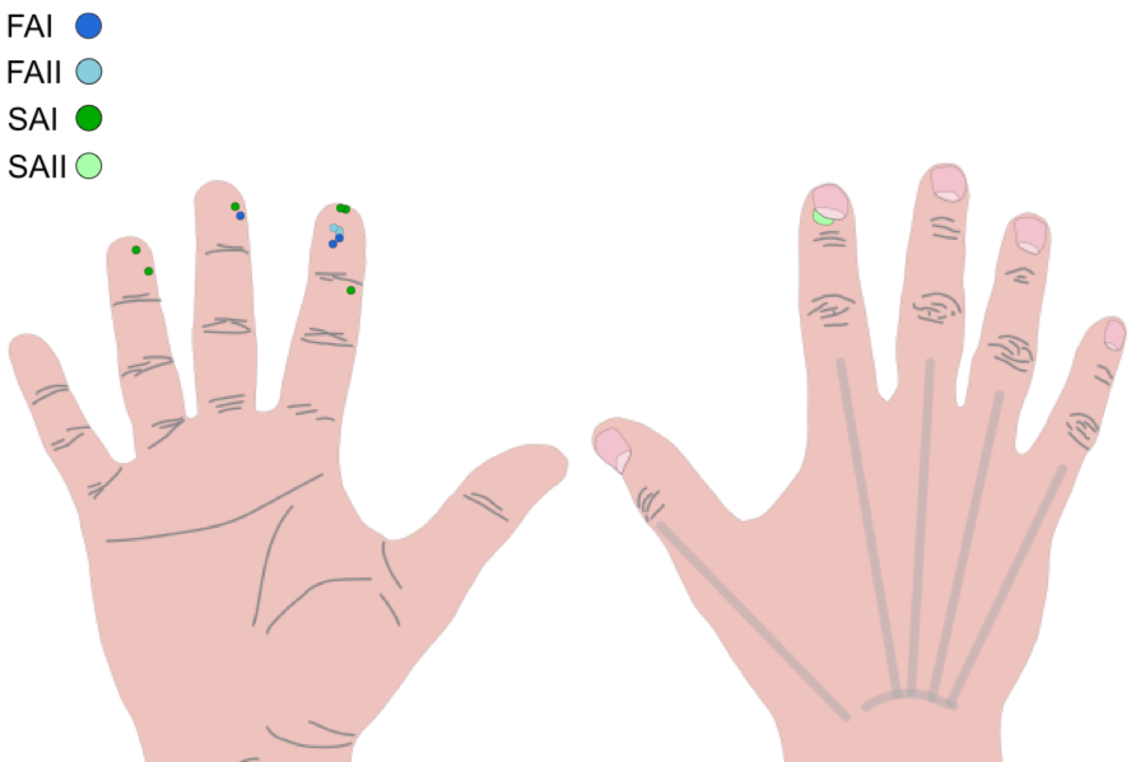


Figure 9 | Type and distribution of single cutaneous mechanoreceptive afferent hot spots recorded from the median nerve at wrist for experiment two. Each dot represents the approximate location and shape of the unit's hot spot. Data collected from both the left and right median nerve are collapsed into a single image for illustrative purposes.

the touch displacement. The fourth panel depicts spike count histograms for 30 ms bins, starting at the displacement onset (0 ms), summed from all 10 trials.

The data displayed in Figure 10 arises from a FAI unit located in the distal phalanx of digit III, on the lateral side. As can be seen, the unit remained quiescent prior to the onset of the touch displacement, despite the tonic application of a light force. For touch displacements that pulled the contact surface away from the participant (Fig. 10A), the unit became active with the displacement onset, remained active for the duration of the stimulus, and continued to discharge for up to 20 ms after the termination of the stimulus. A similar response was observed when the contact surface was pulled towards the participant (Fig. 10B), but with a modestly lower firing frequency and briefer period of post-stimulus activity.

The data displayed in Figure 11 arises from a FAII unit located in the distal phalanx of digit II, in the center of the finger pad. As with the FAI unit described above, the FAII unit remained quiescent while a static light touch force of more than 0.5 N was applied. The unit became active with the onset of the touch displacement away from the participant and remained consistently active throughout the stimulus (Fig. 11A). As with the FAI unit, this FAII unit continued to discharge for a period after the stimulus. In contrast, in response to displacements of the contact surface towards the participant, this FAII unit exhibited an initial period of higher activity with stimulus onset, which then decreased as the stimulus continued (Fig. 11B). This FAII unit ceased firing when the stimulus ended.

Figure 12 displays the data from a SAI unit that was located in the tip of the distal phalanx of digit II. In contrast to the FA units described above, this SAI unit had a low level of sustained activity prior to the onset of the touch displacement, while the finger was in contact with the touch surface. The activity of the unit increased with the onset of the touch displacement away from the participant and remained higher for the duration of the stimulus but returned to a lower level of activity when the stimulus ended (Fig. 12A). In addition, the overall firing rate of the afferent during the stimulus was demonstrably lower than the firing rate observed for the FA units. With a stimulus in the opposite direction, touch displacement towards the participant, this unit demonstrated initial increase in firing with stimulus onset, that then progressively decreased throughout the stimulus duration, but with a sustained higher firing rate for up to 30 ms after the stimulus ended (Fig. 12B).

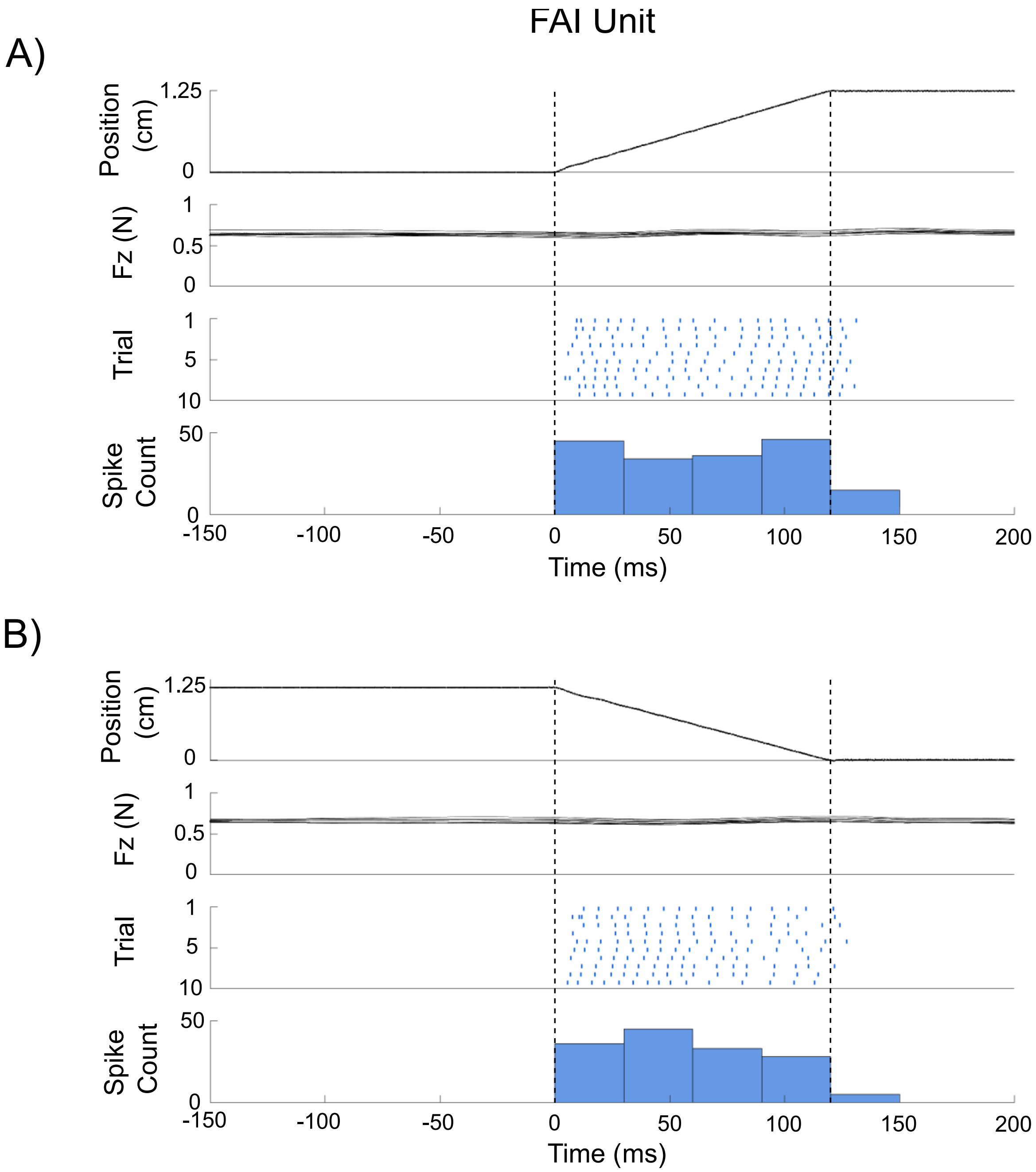


Figure 10 | Representative data recorded from an afferent serving a FAI mechanoreceptor. Data captured during touch displacements A) away from, and B) towards the participant. The top panel of each figure depicts the anterior-posterior position of the touch surface. The second panel displays the load applied to the contact surface for each of the trials overlaid. The third panel displays a raster plot of the discriminated afferent spikes, with each row representing one trial, aligned to the onset of the displacement. The fourth panel is a peri-event time histogram depicting the total number of spikes within 30 ms bins, summed across the ten trials. Vertical dashed lines indicate the start and end of the touch displacement stimulus.

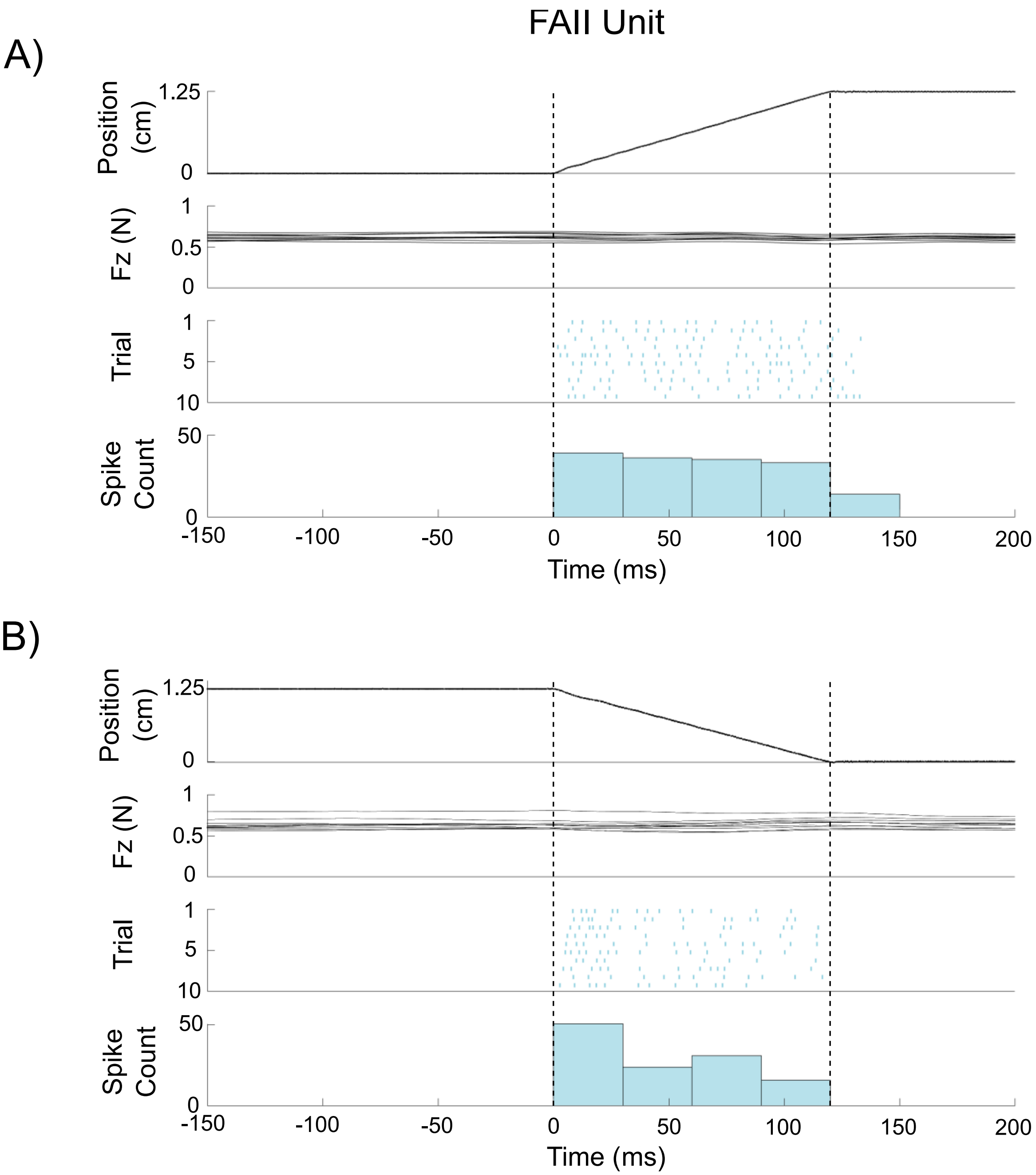


Figure 11 | Representative data recorded from an afferent serving a FAII mechanoreceptor. Data captured during touch displacements A) away from, and B) towards the participant. The top panel of each figure depicts the anterior-posterior position of the touch surface. The second panel displays the load applied to the contact surface for each of the trials overlaid. The third panel displays a raster plot of the discriminated afferent spikes, with each row representing one trial, aligned to the onset of the displacement. The fourth panel is a peri-event time histogram depicting the total number of spikes within 30 ms bins, summed across the ten trials. Vertical dashed lines indicate the start and end of the touch displacement stimulus.

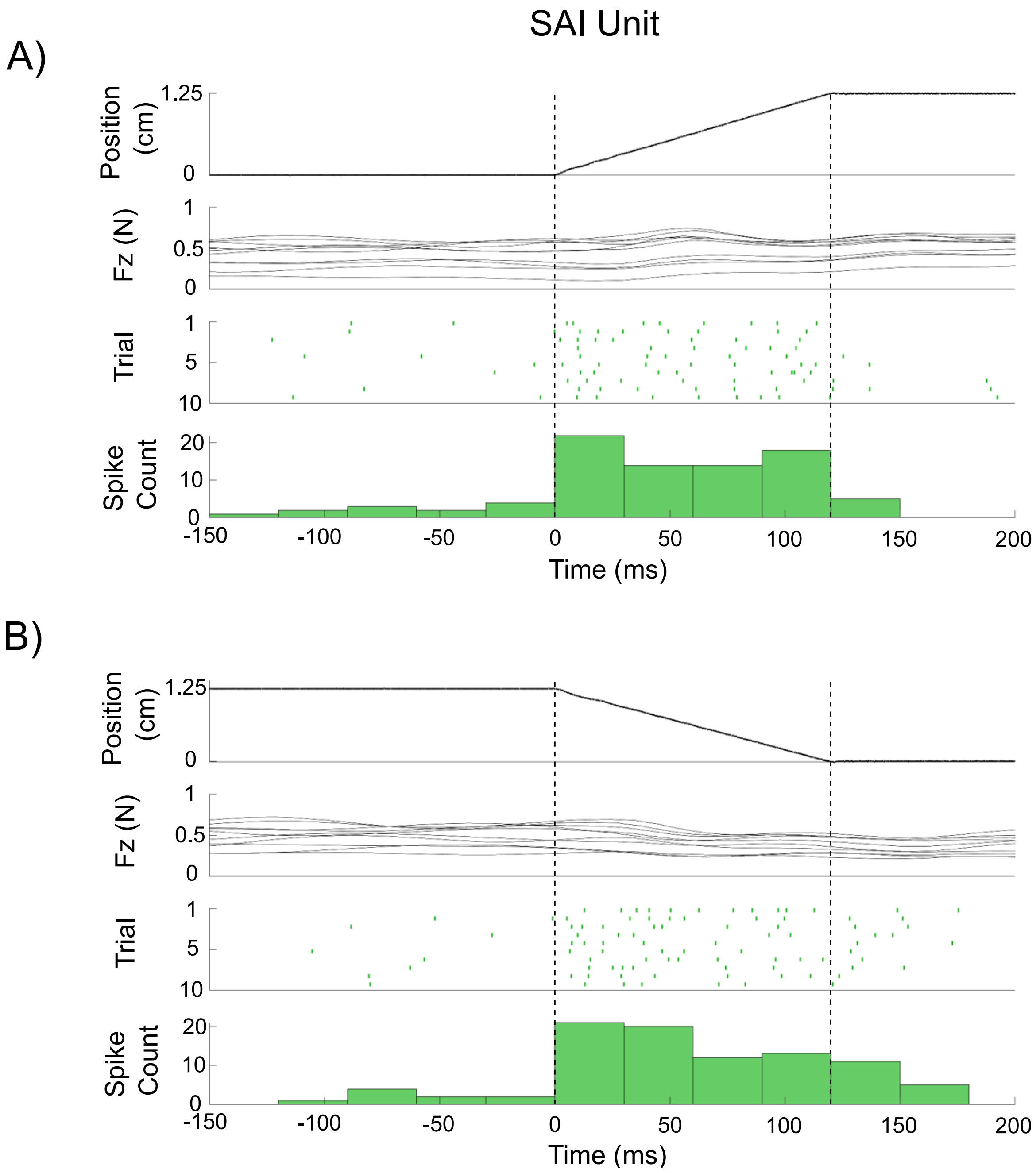


Figure 12 | Representative data recorded from an afferent serving a SAI mechanoreceptor. Data captured during touch displacements A) away from, and B) towards the participant. The top panel of each figure depicts the anterior-posterior position of the touch surface. The second panel displays the load applied to the contact surface for each of the trials overlaid. The third panel displays a raster plot of the discriminated afferent spikes, with each row representing one trial, aligned to the onset of the displacement. The fourth panel is a peri-event time histogram depicting the total number of spikes within 30 ms bins, summed across the ten trials. Vertical dashed lines indicate the start and end of the touch displacement stimulus.

The general afferent activity patterns described above for the three cutaneous mechanoreceptor types were representative of the activity observed across all the units recorded. In Figure 13, the spike counts, such as those depicted in Figures 10 through 12, have been converted to firing frequencies using a 10 ms window for all of the recorded units, and then averaged for each of the unit types. Figure 13A depicts the data arising from touch displacements away from the participant. As can be seen, all three cutaneous mechanoreceptor types became active with the onset of the stimulus and remained more active than baseline throughout the stimulus. However, the specific firing patterns differed. For example, the FAI afferents had an initial peak of activity that ebbed through the middle period of the stimulus, before a second peak of activity at the end of the stimulus. The FAII afferents displayed a relatively stable increase in activity for most of the stimulus duration. Both FA types continued to be active for a brief period after the end of the stimulus. The low level tonic activity in the SAI afferents with the static light touch is apparent in the group averaged data. With the onset of the stimulus there is an initial peak of activity that progressively decreases across the duration of the stimulus and is sustained, gradually decreasing, for a period of time after the end of the stimulus. Figure 13B depicts the average data arising from touch displacements towards the participant from the same afferents as shown in Figure 13A. As with the displacements away from the participant, all of the recorded afferents showed an increase level of activity with the onset of the displacement towards the participant. The average activity in the FAI and SAI units is very similar regardless of the direction of the stimulus. However, the FAII units display a different pattern of activity, depending on the direction of the applied stimulus. For example, the FAII units are robustly activated with the onset of the displacements towards the participants with a sharp decrease in firing frequency for much of the remainder of the stimulus. Moreover, the FAII units have a sharp offset of activity, corresponding with the end of the touch displacement towards the participant.

Rapid Light Touch Displacements Over the Second Digit

To determine if remote cutaneous mechanoreceptors would be activated by the touch displacements, we also applied touch displacement stimuli to the distal phalanx of the second digit when the identified unit was located elsewhere. None of the units with mechanoreceptors located in other regions of the hand were activated by the touch displacement stimulus applied to the distal phalanx of the second digit. This included the SAI unit located near the crease between the distal and middle phalanxes of the second digit and the SAII unit located in the nail bed of the second digit (Figure 9).

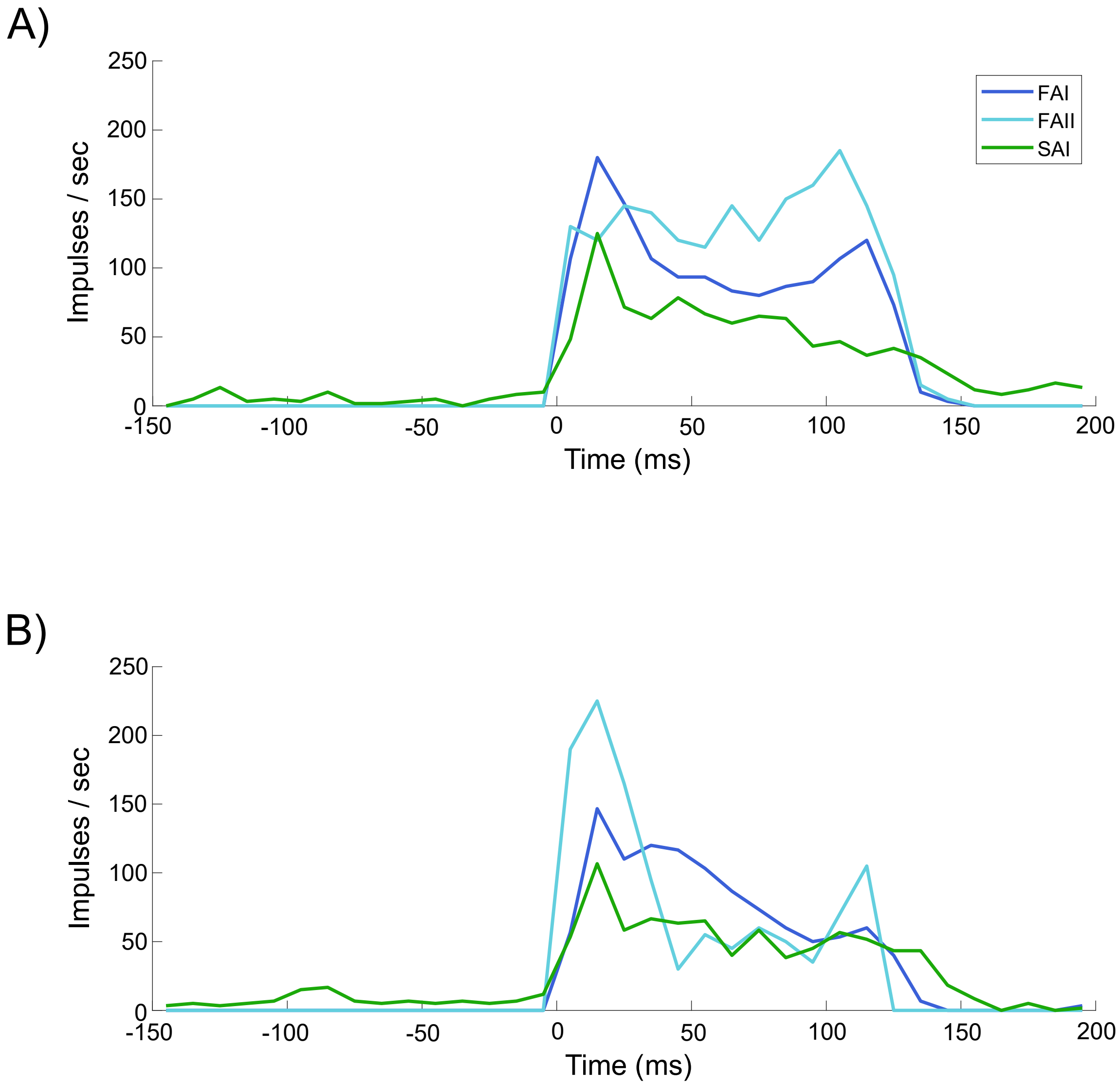


Figure 13 | Firing frequency of each unit type averaged across recorded units. Data for touch displacements A) away from and B) towards the participants. The data from each unit were averaged in 10 ms bins prior to averaging across the group.

Discussion

The aim of Part one was to determine if single cutaneous afferents of the median nerve were capable of influencing motoneuronal pool activity of muscles of the lower limb at a short latency of <120 ms. Indeed, we have demonstrated for the first time rapid interlimb responses in both the TA and SOL muscles relative to the activity of single cutaneous afferents of the median nerve. It was further hypothesized and tested in Part two, that type I cutaneous afferents would show a greater firing frequency than type II afferents in response to rapid displacements of a light touch contact across the receptive field due to their demonstrated local slip sensitivity (Johansson & Westling, 1987). The second hypothesis was not supported as we have demonstrated that all of the single afferents in the glabrous skin of the hand become active and remain active throughout the rapid displacement of a light touch contact moving across an afferent's receptive field.

Interlimb Responses

All four of the afferent types that innervate the glabrous skin of the hand (FAI, FAII, SAI, and SAII) demonstrated interlimb responses in both TA and SOL at latencies less than 120 ms. This suggests that cutaneous afferents from the hand consistently form interlimb connections with muscles of the lower limb and at latencies that would implicate spinal-mediated pathways. In our study, we also observed a higher incidence rate with which activity in single cutaneous afferents modulate muscle activity than what was previously demonstrated for interlimb coupling (foot to hand, Bent & Lowrey, 2013) using a similar STA approach. In particular, Bent & Lowrey (2013) reported interlimb synaptic coupling to upper limb muscles for 67% of FAI cutaneous afferents from the foot. In contrast, we observed 80% of recorded FAI afferents from the median nerve modulated activity in the muscles of the lower leg. Our 80% of FAI afferents that demonstrated interlimb coupling with lower limb muscles is comparable to the 81% of FAI afferents that demonstrated coupling between afferents of the sole of the foot and the muscles of the lower limb (Fallon et al., 2005). Moreover, we demonstrated higher rates of synaptic coupling for FAII, SAI and SAII than what has been observed in previous studies of intralimb (McNulty & Macefield, 2001; Fallon et al., 2005) or interlimb (Bent & Lowrey, 2013) coupling. The higher rate of identifying coupling between single afferents and motor pools in our study might be attributed to having recorded EMG activity from more muscles for each recorded afferent than previous studies, as modulation of activity in a single muscle would identify the afferent was coupled. Alternatively, the increased expression of synaptic coupling could reflect a functionally meaningful higher representation for the sensorimotor connections from the hand to the foot. Nevertheless, our data demonstrate that the majority of cutaneous afferents in the median nerve modulate motor activity of muscles of the ankle at latencies consistent with spinal-mediated pathways.

Previous work had clearly demonstrated that sensorimotor connections exist between the cutaneous afferents of the upper limb and motor pools of the lower limbs. For example, Delwaide & Crenna (1984) used transcutaneous electrical stimulation of the fingers to evoke interlimb cutaneous reflexes in the motor pool of SOL. Moreover, the latencies of the responses demonstrated with the STA approach used presently and previous studies using transcutaneous electrical stimulation are very similar (Zehr et al., 2001), suggesting that the mediating neural circuitry involved is consistent between approaches. An important finding from the present study is that all 4 types of sensory afferents evoked modulation in TA and SOL motor activity, indicating that the complex waveform of electrically evoked cutaneous reflexes likely arises from the convergence of multiple influences on the motor pools.

Touch Displacement Induced Afferent Activity

In Part two of my thesis, rapid displacements of a light touch contact across the receptive field of FAI, FAII, and SAI afferents produced an increase in the firing rate, relative to baseline, of all afferents. Therefore, as hypothesized, both fast and slow adapting type I afferents responded to the light touch displacement, consistent with previous work involving slips (Johansson & Westling, 1987). However, in contrast to my hypothesis, fast adapting type II afferents also demonstrated a clear increase in firing in response to the stimulus. This lack of specificity in the response properties of the recorded afferents contrasts previous work that demonstrated the different afferent types from the glabrous skin of the hand exhibit distinct behaviors in response to touch contact displacement. For example, SA receptors demonstrated directional preferences to slip stimuli (Srinivasan, Whitehouse, & LaMotte, 1990) and roles in tactile directional sensibility (Olausson et al., 2000). Furthermore, FA afferents, in general, demonstrated sensitivity to signal dynamic events (Knibestöl & Vallbo, 1970), while FAII units were specifically shown to be highly sensitive to acceleration (Johansson & Vallbo, 1983). Therefore, it was somewhat unexpected that all of our recorded afferents demonstrated an increase firing rate with the touch displacement, regardless of the direction of motion across the receptive field. Nevertheless, as shown in Fig. 13, the recorded afferents were not monolithic in their response patterns. Indeed, the FA afferents, in particular the FAII afferents, behaved somewhat uniquely, depending on the direction of the stimulus. Moreover, all of the afferents appeared to be sensitive to the onset of the stimulus, with then different characteristics during the steady-state of the stimulus. These differences suggest that each of the afferent types is activated by the displacement of the touch reference, but that each encodes different characteristics of the stimulus, similar to what was previously described with finger slips during precision grip tasks (Johansson & Westling, 1987; Westling & Johansson, 1987). A more detailed evaluation of the stimulus parameters, for example, by varying acceleration, velocity, distance, and direction might elucidate the unique features of the stimulus encoded by the afferents. In addition, our study had a relatively low sample size of afferents from the glabrous skin across the afferent types (FAI=3, FAII=2, SAI=6, SAII=0), limiting the ability to draw comparisons across afferent types. Nevertheless, our study demonstrated that displacement of a light touch reference across the glabrous skin of the hand activates a broad array of sensory feedback that likely represents different parameters of the complex stimulus.

An important finding of the present study was that none of the recorded afferents were activated by a light touch displacement across the pad of the index finger if the receptive field for the afferent was not directly stimulated by the displacement. This indicates that the physical translation of the contact surface across the skin does not result in broad activation of tactile receptors throughout the hand, suggesting location specificity of the evoked sensory feedback. Indeed, a SAI afferent with a receptive field located in the distal portion of the middle phalanx of the index finger was not activated by the stimulus applied only millimeters more distally across the pad. Moreover, the SAII afferent located at the nailbed of the index finger was also not activated by the stimulus applied to the pad. However, we cannot exclude the possibility that displacement of the touch surface across the pad of index activates distant receptors as our sample of afferents was small and largely related to receptors located in the distal phalanx. Therefore, we cannot discount the possibility that cutaneous receptors located in more proximal regions of the hand, or in the hairy skin across joints of the hand, are activated by the translation of the contact surface across the pad of the index finger. Indeed, it has been previously demonstrated that FAII afferents, with receptive fields located in the palm of the hand, are responsive to stimuli applied to the fingertips (Johansson & Westling, 1987). Moreover, we cannot exclude the possibility that other sensory modalities, such as muscle stretch receptors, are activated by the mechanical events or vibrations introduced by the stimulus. Further studies that recorded from the median nerve proximal to muscles of the forearm would need to be performed to better understand the potential role of muscle-based afferents in detecting displacements of a light touch reference.

In our study, across both Parts 1 and 2, we recorded from 51 classifiable afferents in the median nerve at the wrist. These included 18 FAI units, 7 FAII units, 19 SAI units, and 7 SAII units. In addition, 40 of these afferents served receptors located in the fingers and 11 from the palm. This distribution of afferent types within the median nerve and the location of their receptive fields is comparable with previous reports (Johansson & Vallbo, 1979b; Johansson & Vallbo, 1983) and indicates that our methods for identification and classification of afferents was consistent with that of previous studies (Hagbarth, Hongell, Hallin, & Torebjörk, 1970; Knibestöl & Vallbo, 1970; Vallbo & Hagbarth, 1968). However, it is worth noting that in Part two the afferents that could be included in the study were restricted to those that had receptive fields that could be accessed by the touch displacement device. Therefore, afferents located towards the palm were excluded and this then also limited the opportunity to record from type II afferents for that part of the study. Consequently, this study is able to provide strong evidence that all afferent types from throughout the sensory territory of the median nerve form intersegmental connections with the motor pools of the ankle muscles, but can provide only incomplete evidence as to the firing characteristics of these afferents in response to a light touch displacement.

Functional Implications

The primary finding of this study is that afferents of the median nerve serving cutaneous receptors of the hand are synaptically coupled with motor pools of the ankle muscles. The latency of these connections suggests a spinal-mediated circuitry consistent with previous studies investigating electrically evoked intersegmental reflexes (Delwaide & Crenna, 1984; Zehr et al., 2001). Moreover, these latencies are consistent with the onset of rapid balance corrective responses evoked in ankle muscles during standing, following unexpected displacement of a light touch reference (Misiaszek et al., 2016). Taken together, these results suggest that the activation of cutaneous receptors in the glabrous skin of the hand can initiate a complex, intersegmental balance correction at latencies of less than 100 ms. This is further supported by our finding that the recorded afferents were each activated by a light touch displacement over their receptive field, indicating that a rich source of sensory information is available to generate and control these complex balance corrections.

It is well documented that light touch (<1 N) at the finger reduces postural sway (Jeka, 1997), can entrain sway to oscillations of a touch reference (Wing et al., 2011), and can trigger short-latency balance reactions in the ankle muscles (Misiaszek et al., 2016). This evidence suggests that cutaneous information from the hands is integrated into and is functionally coupled to muscles involved in balance control. Indeed, the results from this thesis indicate that all cutaneous sensory modalities form intersegmental connections that could contribute to this effect. The implication is that the use of the hands for balance control, in addition to providing additional mechanical support, provides rich sensory inputs for the integration and control of balance. In turn, this knowledge will help to better understand the control of balance when the hands are used for additional stability, such as with the use of mobility devices. When using mobility aids such as canes or walkers, the user receives continuous cutaneous stimulation when holding these devices. Mobility aids are typically thought to aid balance control mechanically, by increasing the base of support or supporting one's weight (Bateni & Maki, 2005; Joyce & Kirby, 1991). However, the cutaneous feedback from the hands in contact with the mobility aids could also provide sensory feedback to detect the current state of stability or any disturbances to this additional mechanical support. Indeed, if the mobility aid was to slip or snag on an obstacle, cutaneous feedback from the hands could be critical in detecting and correcting for the unexpected instability. Augmenting sensory feedback from the hands during mobility aid use might be one way to improve balance control for those who use such devices. For example, Priplata et al. (2006) demonstrated that augmenting tactile stimulation from the soles of the feet, by use of a specialized shoe insole, increased stability in people with diabetic neuropathy. This suggests that grip design, for example, could play an important role in enhancing sensory feedback from the hands related to balance control. The results from the current study suggest that the cutaneous afferents of the hand are well suited for rapidly conveying balance-related sensory information and that all cutaneous types modalities could be involved.

Technical Considerations

Previous studies of single cutaneous afferent connectivity to motor pools typically observed cyclic modulation of activity in the STA EMG traces (Bent & Lowrey, 2013; Fallon et al., 2005; McNulty & Macefield, 2001; McNulty et al., 1999). We did not observe such cyclic modulations in our study. This difference arises from the different methodological approaches used between the studies to activate the cutaneous afferents. Previous studies used vigorous brushing or stroking across the receptive field to activate the afferents (Bent & Lowrey, 2013; Fallon et al., 2005; McNulty et al., 1999), resulting in cyclic EMG responses that appear to be related to afferents that exhibit a regular discharge pattern (McNulty & Macefield, 2001; McNulty et al., 1999). This results in EMG deflections that are not related to the reference spike, but to spikes preceding or following the reference spike within a train and can result in the appearance of EMG responses at physiologically unrealistic short latencies. We purposely attempted to avoid this effect and therefore chose instead to use a series of stochastic taps to activate FA afferents and sustained application of pressure to activate SA afferents, and consequently did not observe any cyclic EMG responses.

Stimulating single cutaneous receptors in situ is unrealistic. Therefore, it is quite likely that while activating the receptors of the recorded afferents, a number of additional nearby receptors were also stimulated. Activating multiple receptors is especially likely when taking into account the density of cutaneous innervation in the fingers and hands, the small receptive field sizes of type I afferents, and their high sensitivities (Johansson & Vallbo, 1979a, 1979b; Johansson & Vallbo, 1983). Therefore, it is possible that the synaptic coupling identified in the STA EMG traces arose from the activation of an afferent other than the one that was being recorded. However, firing from confounding afferents that are not strictly aligned with the referent afferent will result in the cancelation of the otherwise stochastic EMG signal. To influence the EMG trace produced by the averaging of hundreds of traces the firing pattern of the confounding afferent would need to present with substantial overlap to the referent afferent, and this seems unlikely.

The technique used for investigating interlimb single unit connectivity, STA, is a simple approach that has been used in similar experiments (Bent & Lowrey, 2013; Fallon et al., 2005; McNulty & Macefield, 2001; McNulty et al., 1999; Zehr et al., 2001). Spike-trigger averaging to the activity of a single afferent decreases the chances of the activity from other afferents influencing the averaged trace, and has historically been used to investigate synaptic coupling within the CNS to motoneuron pools of peripheral muscles (Gandevia, Burke, & McKeon, 1986). However, this technique only provides information on the average activity from an ensemble of spikes, therefore it is possible for nuances among the signal to exist, but not be detected. However, this potential limitation of the STA approach is not a major concern presently as the purpose of our study was to demonstrate rapid interlimb responses between cutaneous afferents of the median nerve and motoneuron pools of ankle muscles, which this technique is well-suited to address.

Microneurography has been an important technique to gain insight into the peripheral nerve function of awake humans. However, given the size of the electrode relative to the nerve, it has been suggested a conduction block at the site of the electrode insertion is possible (Wall & McMahon, 1985). Conduction block could arise due to pressure at the site or from a potential electrical short, resulting in the failure of action potential conduction beyond the site of the recording. Although conduction block is possible, the risk is generally considered low (Vallbo 1976). In addition, it is suggested that the appearance of a second peak in the action potential and an increase in the latency are indicators of an impending conduction block (Inglis et al., 1996), which can therefore be avoided. Therefore, conduction block was not a major concern during these experiments. Indeed, the majority of afferents recorded resulted in significant modulation of STA EMG activity, indicating that afferent activity was conducting past the recording site.

Future Directions

The main findings from this thesis are, 1) all four afferent types that innervate the glabrous skin of the hand (FAI, FAII, SAI, and SAII) demonstrated interlimb responses in both the TA and SOL at latencies less than 120 ms; and 2) all recorded cutaneous afferents increase their firing when a touch contact moves across their receptive field. This evidence suggests that cutaneous afferents from the hand are capable of contributing to balance corrective responses elicited following a rapid and unexpected displacement of a light-touch reference (Misiaszek et al., 2016). However, an obvious and distinct differentiation in afferent sensitivity to the touch contact displacement was not observed, contrary to previous evidence arising from slip stimuli (Johansson & Vallbo, 1983; Srinivasan et al., 1990; Westling & Johansson, 1987). It is possible that the characteristics of the stimulus we used, which mimicked the touch displacement used by Misiaszek et al. (2016), were uniquely poised to mask afferent-related differences in detection of stimulus properties. Therefore, it would be important to perform an additional study that specifically varied the stimulus parameters, including direction, acceleration, and velocity of the displacement, as well as the level of vertical load, to determine if the differences noted with previous studies are related to the nature of the touch displacement or perhaps the nature of the light touch itself. Knowledge of how the different sensory modalities are activated by a balance-related light touch stimulus could be useful information for the improved design of mobility devices to aid populations at high risk of falling.

In this study, STA was used to investigate potential interlimb responses between cutaneous afferents of the median nerve and motoneuron pool excitability in muscles of the lower limb. STA is an approach that allows for analyses in the temporal domain, such as was used here. However, analysis in the frequency domain could potentially draw out more complex patterns of connectivity, which could lead to a deeper understanding of the interlimb responses we have demonstrated. Investigating the frequency domain could help determine if there are any time varying dependencies in the interlimb responses, such as the frequency of afferent discharge influencing the EMG patterns generated. The pattern of afferent discharge can be influenced by the physical stimuli applied, and therefore by changing the physical stimuli the likelihood of observing interlimb responses could be increased. This, in turn, could provide more detailed information about the role of the different sensory modalities activated by balance-related light touch and further enhance the integration of this knowledge into the design of mobility aids that improve balance control.

Conclusion

For the first time, we have demonstrated that single cutaneous afferents of the hand innervated by the median nerve are capable of making short latency (<120 ms) connections to muscles of the lower limb. Moreover, we have demonstrated that all 4 types of mechanoreceptors form these spinal, intersegmental connections. In addition, we have also demonstrated that these cutaneous mechanoreceptors in the hand are each activated by rapid displacement of a light touch contact across their receptive field. Taken together, these results demonstrate that light touch of a stable reference activates richly diverse sensory feedback that influences activation of muscles involved with standing balance, at latencies sufficient to initiate spinal-mediated balance corrections. Importantly, these cutaneous afferents exist in the hand a readily available sensory system known to be important in balance control (Holden, Ventura, & Lackner, 1994; Jeka, 1997; Jeka & Lackner, 1994). Falls can have devastating consequences and are an increasing concern as our population continues to age (Masud & Morris, 2001; Murray et al., 2012; Spaniolas et al., 2010). By further delineating the ability for cutaneous information to influence balance control, future technologies can be developed to improve quality of life for those with balance impairments, and reduce time and money spent on hospitalization and rehabilitation for those who have suffered a fall.

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Appendix

The following is a summary table of number of experiments, number of active electrodes used per experiment, adverse effects, and time for adverse effects to resolve. Single unit cutaneous activity was searched for in every experiment. Experiments were performed on median nerve at wrist, approximately 2 cm proximal to the wrist crease, typically between the tendons of palmaris longus and flexor pollicis longus. In only one instance the experiment was stopped immediately due to participant discomfort - not included in table.

Experiment Number	# of Active Electrodes Used	Adverse Effects
		Interlimb Experiments
1	1	No
2	2	Paresthesia about the receptive field of recorded afferent evoked when the joint is moved into an extreme position and the nerve is stretched. Resolved after 2 weeks.
3	1	No
4	1	No
5	1	Paresthesia about the receptive field of recorded afferent evoked when the joint is moved into an extreme position and the nerve is stretched. Resolved after 2 weeks.
6	1	No
7	1	No
8	1	No
9	1	No
10	1	No
11	2	No
12	2	No
13	1	No
14	1	No
15	1	No
16	1	No
17	1	No
18	1	No
19	1	No
20	1	No
21	2	No
22	2	No
23	2	No
24	1	No

25	1	Slight swelling and bruising at site of active electrode insertion. Resolved after 1 week.
26	1	Strong feelings of sharp pain upon insertion of reference electrode, which quickly subsided.
27	2	No
28	2	Redness at site of active electrode insertion. Resolved in few days.
29	1	No
30	2	No
31	2	Paresthesia about the receptive field of the afferent recorded which lasted for approximately one hour after experiment.
32	3	No
33	2	Slight bruising at site of active electrode insertion. Resolved <1 week.
34	2	No
35	1	No
36	2	No
37	1	No
38	1	No
39	3	No
40	1	No
41	1	No
42	1	No
	Light-Touch Displacement Experiments	
43	2	No
44	1	Slight sensitization at site of active electrode insertion. Resolved <1 week.
45	1	No
46	2	No
47	2	Slight sensitization at site of active electrode insertion. Resolved in a few days.
48	2	Slight sensitization at site of active electrode insertion. Resolved in a few days.
49	1	No
50	2	No
51	1	Slight sensitization at site of active electrode insertion. Resolved in a few days.
52	1	No
53	1	No
54	2	Slight sensitization at site of active electrode insertion. Resolved few days later.
55	2	No

Total Active Electrodes Used	79
Adverse Effects Resolved <1 Week	9/12
Adverse Effects Resolved 1-2 Weeks	3/12
Total Resolved Adverse Effects	12/12