Title: Cutaneous afferent innervation of the human foot sole: What can we learn from single unit recordings?

Call: 50 Years of Microneurography: Insights into Neural Mechanisms in Humans

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Running Head: Cutaneous afferents of the human foot sole

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Abstract: Cutaneous afferents convey exteroceptive information about the interaction of the body with the environment, and proprioceptive information about body position and orientation. Four classes of low threshold mechanoreceptor afferents innervate the foot sole and transmit feedback that facilitates the conscious and reflexive control of standing balance. Experimental manipulation of cutaneous feedback has been shown to alter the control of gait and standing balance. This has led to a growing interest in the design of intervention strategies that enhance cutaneous feedback and improve postural control. The advent of single unit microneurography has allowed the firing and receptive field characteristics of foot sole cutaneous afferents to be investigated. In this review, we consolidate the available cutaneous afferent microneurographic recordings from the foot sole and provide an analysis of the firing threshold, and receptive field distribution and density of these cutaneous afferents. This work enhances the understanding of the foot sole as a sensory structure and provides a foundation for the continued development of sensory augmentation insoles and other tactile enhancement interventions.

News and Noteworthy: We present a synthesis of foot sole cutaneous afferent microneurography recordings, and provide novel insights about the distribution, density, and firing characteristics of cutaneous afferents across the human foot sole. The foot sole is a valuable sensory structure for the control of standing balance, and our findings provide a new understanding on how the foot sole can be viewed as a sensory structure.

Introduction

Four classes of low threshold cutaneous mechanoreceptors innervate the glabrous skin on the sole of the foot and palm of the hand. Each class is uniquely sensitive to deformation and motion of the skin and transmits tactile and proprioceptive feedback through sensory afferents to the central nervous system (CNS) (McGlone and Reilly, 2010). The development of microneurography in the 1960s by Hagbarth and Vallbo permitted the study of single cutaneous afferents in awake human subjects (Hagbarth and Vallbo, 1967; Vallbo et al., 2004). The technique was originally developed in the arm, and the understanding of cutaneous afferent firing and receptive field characteristics is largely a product of these early studies that investigated afferent recordings from the hand (Hagbarth et al., 1970; Knibestöl and Vallbo, 1970; Johansson and Vallbo, 1979a). The same classes of mechanoreceptor afferents as those described in the hand innervate the foot sole (Miller and Kasahara, 1959; Kennedy and Inglis, 2002); however, fewer studies have recorded cutaneous afferents in the lower limb. To understand the functional role of cutaneous feedback, the distribution and firing thresholds of individual cutaneous afferents across the body must first be assessed. In this review, we summarize microneurographic recordings made from several populations of foot sole cutaneous afferents. We provide an analysis of mechanoreceptor firing thresholds and receptive field characteristics, as well as provide afferent distribution and density calculations.

Why study foot sole cutaneous afferents? Cutaneous feedback from the soles of the feet plays an important role in the control of gait and standing balance (Kavounoudias et al., 1998; Inglis et al., 2002; Zehr et al., 2014). Skin stretch and pressure feedback associated with standing balance are conveyed by cutaneous afferents into the central nervous system (CNS) where it interacts with descending motor commands at the spinal cord and reflexively modulates motor neuron excitability (Zehr and Stein, 1999; Fallon et al., 2005; Bent and Lowrey, 2013). Furthermore, cutaneous feedback provides proprioceptive cues at the ankle joint (Lowrey et al., 2010; Howe et al., 2015; Mildren et al., 2017) and a sense of body movement with respect to the ground (Kavounoudias et al., 1998). In situations where this cutaneous feedback is impaired, either experimentally through cooling (Eils et al., 2004), local anaesthesia (Meyer et al., 2004a) or naturally through ageing (Perry, 2006; Peters et al., 2016) and disease (Prätorius et al., 2003; Kars et al., 2009), the control of standing balance is compromised. To fully understand how afferent feedback can contribute to the control of standing balance, we must first establish the capabilities of foot sole cutaneous afferents to respond to tactile input.

Previous work has thoroughly presented the specialization of each mechanoreceptor ending with associated afferent firing properties in the hand (Macefield, 1998; Johnson, 2001). The hand and feet contain the same classes of mechanoreceptor endings and detailed descriptions of these endings can be found in previous studies (Loewenstein and Skalak, 1966; Chambers et al., 1972; Fortman and Winkelmann, 1973; Iggo and Andres, 1982; Abraira and Ginty, 2013). The objective of the current review is to provide a physiological summary of a selection of microneurographic recordings made from cutaneous afferents innervating the human foot sole.

We have compiled the published tibial nerve cutaneous afferent recordings available in the literature (Kennedy and Inglis, 2002; Fallon et al., 2005; Lowrey et al., 2013; Strzalkowski et al., 2015a), in addition to 72 unpublished foot sole units. From the 401 units identified, 364 were in the plantar surface of the foot sole and form the basis of the analysis in this review. We begin with a brief description of the technique of microneurography and review how the four classes of cutaneous afferents were collected and classified. Next, we summarize the foot sole cutaneous afferent literature and provide new insights highlighting afferent firing threshold, receptive field characteristics and distribution, as well as provide the first estimates of foot sole innervation density.

Microneurography: Single unit recordings

Signals provided between individual neurons represent the fundamental mechanism for information transfer in the nervous system (Parker and Newsome, 1998). Microneurography is a method to record peripheral nerve activity in awake human subjects and provides a tool to link neural activity with functional outcomes. The original technique was developed in Uppsala Sweden by Karl-Erik Hagbarth and Åke Vallbo between 1965 and 1966, with the initial interest to study human muscle spindles from multi-unit recordings (Vallbo et al., 2004). Since then, microneurography has been applied to the study of cutaneous mechanoreceptor, thermoreceptor and nociceptor afferents, C-tactile afferents, golgi tendon organs, joint receptors, muscle spindles, and cutaneous and muscle sympathetic efferents (Roll and Vedel, 1982; Ochoa and Torebjörk, 1989; Wallin and Elam, 1994; Campero et al., 2001; Hagbarth, 2002; Macefield, 2005; Ackerley et al., 2014; Condon et al., 2014; Pruszynski and Johansson, 2014; Strzalkowski et al., 2016; Peters et al., 2017). The technique was developed in the arm, and the majority of recordings have been made from the forearm and hand; however there is growing interest in studying the lower limb (Ribot-Ciscar et al., 1989; Trulsson, 2001; Kennedy and Inglis, 2002; Aimonetti et al., 2007; Bent and Lowrey, 2013; Lowrey et al., 2013; Strzalkowski et al., 2015a).

Microneurography involves the percutaneous insertion of two tungsten microelectrodes: one reference, placed a few millimetres under the skin, and one recording electrode, manually inserted into a peripheral nerve (Figure 1). The target nerve for foot sole cutaneous afferents is the tibial nerve, and recordings are made at the level of the popliteal fossa where the tibial nerve runs several centimetres below the skin. The tibial nerve divides into three terminal branches distal to the popliteal fossa; the lateral and medial plantar nerves and the medial calcaneal branches (Davis and Schon, 1995). Together these branches innervate the skin on the foot sole with the exception of the far medial arch, which is supplied by the saphaneous terminal branch of the femoral nerve. Tibial nerve microneurography therefore provides a nearly complete picture of foot sole innervation. For detailed reviews on the microneurography technique and applications we recommend: (Gandevia and Hales, 1997; Bergenheim et al., 1999; Hagbarth, 2002; Vallbo et al., 2004).

Overview of cutaneous afferents

Cutaneous mechanoreceptors and their associated afferents are the fundamental units for the transduction and transmission of tactile feedback to the CNS (Johnson, 2001; Abraira and Ginty, 2013; Zimmerman et al., 2014). Cutaneous afferents are distinguished from other sensory systems for their high sensitivity and specificity to mechanical deformations of the skin. When vibration, pressure, or stretch is applied to the skin, mechanical deformations are transmitted through the tissue to the cutaneous afferent mechanoreceptor endings. Cutaneous afferents originate in the dorsal root ganglia and project distally to specialized mechanoreceptor endings within the epidermal and dermal layers of the skin and to central targets within the dorsal horn of the spinal cord and brainstem dorsal column nuclei (Zimmerman et al., 2014). For a detailed review of cutaneous afferent projections and processing see (Abraira and Ginty, 2013).

Four specialized mechanoreceptor endings have been identified that innervate the glabrous skin of the hands (Knibestöl and Vallbo, 1970; Jones and Smith, 2014) and feet (Kennedy and Inglis, 2002). The termination depth and morphology of the different mechanoreceptors dictate the unique firing characteristics exhibited by each cutaneous afferent class (Iggo, 1977; Johnson, 2001; Pruszynski and Johansson, 2014). It is well established that each cutaneous afferent class preferentially encodes distinct tactile stimuli (Johnson, 2001). This specialization allows populations of afferents to convey a wide range of tactile feedback with high resolution. The convergence of fast and slowly adapting afferent information onto neurons in primary somatosensory cortex (Pei et al., 2009; Saal and Bensmaia, 2014)suggests that ultimately groups, rather than single cutaneous afferents or classes are responsible for encoding tactile stimuli beyond simple light touch (Strzalkowski et al., 2015a).

Classification

The combination of sensory nerve and mechanoreceptor ending make the sensory unit, commonly referred to as the cutaneous afferent. When isolated during a microneurographic recording, cutaneous afferents are classified based on their ability to respond to sustained stimuli [fast adapting (FA) or slowly adapting (SA)] as well as their receptive field characteristics (type I or type II) (Knibestöl and Vallbo, 1970; Macefield, 1998; Bergenheim et al., 1999).

FA afferents are sensitive to the rate of change of mechanical stimuli and typically fire throughout the dynamic (acceleration) phase of an indentation, but cease to fire once the indentation is sustained (Knibestöl, 1973; Iggo, 1977). FA afferents generally fire at the onset of a sustained indentation and again once the stimulus is removed. This is referred to as an on-off response. Conversely, SA afferents continue to fire throughout sustained indentations and skin stretch (Iggo, 1977). SAI afferent responses are primarily related to the magnitude of the applied stimulus (Knibestöl, 1975), and encode the strain distribution within the skin, which includes information about edges (Phillips and Johnson, 1981) and curvature (Goodwin et al., 1997). FAI afferents are more responsive to tactile events such as the motion or slippage of an object across the skin, as well as coarse vibrations (Knibestöl, 1973). The specialized adaptation properties of FA and SA afferents to sustained indentations is well established and remains the primary tool for the classification of cutaneous afferents as FA or SA during single unit recordings.

Fast and slowly adapting cutaneous afferents are further classified as type I (FAI and SAI) or type II (FAII and SAII) based primarily on their receptive field characteristics (Johansson, 1978; Vallbo and Johansson, 1984). A receptive field represents the area of skin wherein stimulation (e.g., skin indentation) can elicit a response in a given afferent. First characterized in the hand, receptive fields are traditionally measured as the area over which an afferent responds to an indentation force 4-5 times its firing threshold (Vallbo and Johansson, 1984). This convention has been widely adopted which permits receptive fields to be compared across experiments and body location. Afferent classes display unique receptive fields that arise from the branching pattern of the distal axons and morphology and termination location of the mechanoreceptor ending(s).

Type I afferents branch as they enter the skin and terminate in multiple, small mechanoreceptor endings located in superficial skin layers (Miller and Kasahara, 1959; Vallbo and Johansson, 1978; Abraira and Ginty, 2013). FAI afferents terminate in Meissner corpuscles in the dermal papillae, while SAI afferents terminate in Merkel cells in the basal layer of the epidermis (Macefield, 1998; Abraira and Ginty, 2013). As a result, type I afferents typically have small receptive fields (hand palm ~12 mm^2, foot sole ~78 mm^2) with distinct borders and multiple hot-spots (Johansson and Vallbo, 1980; Kennedy and Inglis, 2002). In the hand, FAI afferents typically contain 12-17 such hot-spots while SAI afferents contain 4-7, which are thought to correspond to the number of mechanoreceptor endings in each class (Macefield and Birznieks, 2009). In contrast, type II afferents do not branch within the skin and innervate a single, relatively large mechanoreceptor in the dermis and subcutaneous tissues. FAII afferents terminate in Pacinian corpuscles and SAII afferents terminate in Ruffini endings (Macefield, 1998; Abraira and Ginty, 2013). In this way type II afferents are classified by their large receptive fields (hand palm ~88 mm^2, foot sole ~560 mm^2), with indiscriminate borders and a single zone of maximal sensitivity (Johansson and Vallbo, 1980; Kennedy and Inglis, 2002). In particular, FAII afferents are exceptionally sensitive to stimuli applied within, but also remote to their receptive fields, highlighted by their distinct ability to respond to blowing across the skin. SAII afferents are unique among the other classes in their sensitivity to respond to skin stretch applied through their receptive fields (Hulliger et al., 1979; Kennedy and Inglis, 2002; Macefield and Birznieks, 2009). The receptive fields of the combined foot sole afferents summarized in this review are presented in Figure 2.

Cutaneous afferents in the foot sole

Previous studies have provided an initial look at the characteristics of foot sole cutaneous afferents (Kennedy and Inglis, 2002; Strzalkowski et al., 2015a; 2017); however low sample sizes have limited the ability to make clear estimates of afferent distribution and density. By combining published and unpublished microneurography recordings this review provides a comprehensive summary of the foot sole cutaneous afferent literature and the first estimate of innervation density.

Methods Overview

We have combined published (Kennedy and Inglis, 2002; Fallon et al., 2005; Lowrey et al., 2013; Strzalkowski et al., 2015a) and unpublished tibial nerve recordings to create a data set of 401 cutaneous afferents. The tibial nerve does not exclusively innervate the glabrous skin on the foot sole, and from this data set of 401 afferents 37 were excluded from analysis because they did not have receptive fields on the sole of the foot. Of these excluded afferents, 23 afferents had receptive fields on the ankle, 4 in the nail bed, 3 on the foot dorsum and 7 afferents did not have locations reported. Calculations of afferent class firing threshold, receptive field size, distribution, and innervation density were made on the remaining sample of 364 foot sole cutaneous afferents (Table 1). All published and unpublished data were collected with approval from their local ethics boards and complied with the Deceleration of Helsinki.

To follow the approach of Johansson and Vallbo (1979), who provided the first and only estimates of the afferent innervation density for the glabrous skin of the hand, we required two pieces of information: an estimate of the total number of cutaneous afferents in the plantar nerves, and area measurements for the different foot sole skin regions. In lieu of cutaneous afferent counts for the plantar nerves, we approximated this value based on the value provided by Johansson and Vallbo (1979) for the whole hand (17,023 units), and the observation that there is approximately one tenth the myelinated fibres in the plantar nerves of the foot than in the median and ulnar nerves of the hand (Auplish and Hall, 1998). This resulted in a total plantar cutaneous fibre estimate of 1,702 units. The sample of 364 foot sole units compiled in this review (Table 1) is sampled across several labs, and multiple microneurographers and is assumed to be a random selection from this population afferents innervating the foot sole. Although we cannot guarantee true randomness of afferent selection, we believe the sample compiled in this review provides an accurate representation of the class ratio and distribution of foot sole cutaneous afferents.

Lastly, to obtain area measurements for the different regions of the foot sole, we optically scanned the plantar surface of the right foot in 8 adults (4 men age 25-31, US shoe size 10-12, and 4 women age 25-28, US shoe size 6-9) (Scanjet 4600; Hewlett Packard, USA), and digitally measured the various areas using ImageJ 1.42q (National Institutes for Health, USA). The foot sole was divided into nine distinct regions: the great toe (GT), digits 2 to 5 (Toes), the medial, middle, and lateral metatarsals (MedMet, MidMet, and LatMet), the medial, middle, and lateral arch (MedArch, MidArch, and LatArch), and the calcaneus (Heel) (Figure 3). These distinct foot regions were used to determine whether the different characteristics of interest (cutaneous afferent firing threshold, receptive field area, distribution, and density) varied by region.

Firing thresholds

Each class is uniquely tuned to different features of mechanical stimuli, which contributes to a comprehensive view of the tactile environment. Previous work in animals (Werner and Mountcastle, 1965; Pubols et al., 1971; Phillips and Johnson, 1981; Bensmaïa et al., 2005; Muniak et al., 2007) and the human hand (Knibestöl and Vallbo, 1970; Johansson and Vallbo, 1979a; Johansson et al., 1982; Hallin et al., 2002; Condon et al., 2014) have led to the current understanding of human cutaneous afferent firing characteristics; and has formed the foundation for more recent experiments in the lower limb (Trulsson, 2001; Kennedy and Inglis, 2002; Aimonetti et al., 2007; Strzalkowski et al., 2015a; 2017). Below we review the firing thresholds recorded from cutaneous afferents in the foot sole (Table 2) and compare these to the hand to provide a more comprehensive look at the potential differences between the two sites.

Monofilament testing is a common technique and standard measure of cutaneous afferent firing threshold. Semmes-Weinstein monofilaments (Collins et al., 2010) come in sets that include filaments of different gauges (length and diameter) that vary logarithmically in the load they apply. When applied perpendicular to the skin, each monofilament buckles and delivers a calibrated force (Collins et al., 2010). Cutaneous afferent threshold testing involves the application of monofilaments to the receptive field hotspot (most sensitive location) to determine the minimal force (threshold) that can reliably (~75%) evoke afferent discharge. Monofilaments only examine afferent light touch threshold, known to be conveyed by the FA afferents (Strzalkowski et al., 2015a), whereas other mechanical stimuli, such as stretch (Aimonetti et al., 2007) and vibration (Strzalkowski et al., 2017), have been used to further characterize the firing characteristics of lower limb cutaneous afferents. These studies have shown SAII afferents to be particularly sensitive to skin stretch and FAII afferents most responsive to high frequency vibration. Despite the availability of other threshold tests, monofilaments remain the most common technique, and the literature provides a large sample of monofilament afferent firing thresholds for comparison.

In the present review, we compiled the afferent monofilament firing thresholds across 1) classes and 2) foot sole region (Figure 4). Afferents with firing thresholds outside ±3 standard deviations of the class mean were excluded (4 units excluded). To determine if differences in mechanical thresholds between afferent classes and skin regions were significant, we performed a 4 (classes) by 9 (regions) factorial ANOVA on the observed threshold values. We observed significant effects of afferent class ($F_{3,311}$ = 11.254, $p < 0.001$) and skin region ($F_{8,311}$ = 2.329, $p = 0.02$), however, there was no class by region interaction ($F_{24,311}$ = 1.547, $p = 0.055$). For afferent class, Turkey post-hoc tests revealed that SAII afferents had higher mechanical thresholds than the other three classes ($p < 0.001$). For the different skin regions, Tukey post-hoc tests additionally revealed that the heel has higher thresholds than the lateral arch and the toes ($p < 0.05$). Regional variation in afferent firing thresholds correspond well with previously reported monofilament (light touch) perceptual thresholds that are consistently found to be highest in the heel (Kekoni et al., 1989; Nurse and Nigg, 1999; Hennig and Sterzing, 2009; Strzalkowski et al., 2015a; 2015b). Across the foot sole FA afferents consistently have lower firing thresholds than SA afferents. Median FAI and FAII afferent thresholds are 0.69 g and 0.5 g, while SAI and SAII afferent thresholds are 1.74 g and 10.0 g respectively. Cutaneous afferent classes in the hand are similarly segregated by firing threshold but at much lower thresholds (approximately 10 fold) than those in the foot sole (hand median FAI 0.06 g, FAII 0.05 g, SAI 0.13 g, SAII 0.76 g) (Johansson and Vallbo, 1980). Differences in firing threshold between hands and feet likely reflect an adaptation to the different functional demands of each region. Low firing thresholds in the hands is advantageous for manipulating objects, while high threshold afferents from the foot sole may better serve the high forces of standing balance. The mechanical properties of the skin can partially explain some differences in firing thresholds between the hands and feet (Strzalkowski et al., 2015a), however it is unclear if regional differences exist between the mechanoreceptor endings themselves. Future studies are needed to explore the firing patterns of cutaneous afferents under natural loaded and/or dynamic conditions.

Receptive field characteristics

Receptive fields are traditionally mapped onto the skin surface using a monofilament that delivers a force four to five times greater than the afferent firing threshold (Vallbo and Johansson, 1978; Johansson and Vallbo, 1980). Receptive field borders are then drawn onto the foot sole by connecting the furthest points from the receptive field hotspot at which an afferent discharge can be evoked. These methods were used for all afferents in the present review (Figure 2 and 5). To determine if differences in RF area between afferent classes and skin regions are significant, we performed a 4 (classes) by 9 (regions) factorial ANOVA on the observed RF area values. We observed significant effects of afferent class ($F_{3,315} = 23.510$, $p < 0.001$) and skin region ($F_{8,315} = 3.643$, $p < 0.001$), as well as a class by region interaction ($F_{24,311} = 2.397$, $p < 0.001$). For afferent class, Turkey post-hoc tests revealed that FAII afferents have larger receptive fields than the other three classes ($p < 0.001$). SAII afferents also have larger receptive fields that FAI afferents ($p < 0.05$). For the different skin regions, Tukey post-hoc tests additionally revealed that the toes have smaller receptive fields than the heel and middle metatarsal regions ($p < 0.05$).

The relationships between receptive field size, afferent class and foot sole location are similar to those reported in the hand, although hand receptive fields are smaller than those in the foot sole (Knibestöl, 1973; 1975; Johansson and Vallbo, 1980). Type II afferents in the foot sole and hand have larger receptive fields (median foot sole FAII 481.1 mm^2, SAII 171.6 mm^2, median hand FAII 101.3 mm^2, SAII 58.9 mm^2) compared to type I afferents (median foot sole FAI 55.0 mm^2, SAI 66.4 mm^2, median hand FAI 12.6 mm^2, SAI 11.0 mm^2) (Johansson and Vallbo, 1980) (Table 2, Figures 2 and 5). The toes and fingers have smaller receptive fields compared to the foot sole and hand palm; which is thought to reflect the physical boundaries of these regions. In the hand, FAI receptive fields have been shown to be 52% and SAI receptive fields 23% smaller in the fingers than the palm (Knibestöl, 1973; 1975). Knibestöl used a glass probe to measure receptive fields and direct area comparisons with the present data is not possible; however, toe receptive fields (median FAI 42.4 mm^2, FAII 71.1mm^2, SAI 51.8 mm2, SAII 137.4 mm^2) are smaller compared to the rest of the foot sole. Receptive field sizes reflect mechanoreceptor size and termination depth and further work is needed to investigate the functional significance of receptive field differences between regions in the foot sole.

In summary, receptive field data provides a valuable way to understand the relative responsive areas between cutaneous afferent classes and regions. Smaller RF enables the potential for greater resolution of tactile feedback. Foot sole receptive fields are found to be larger than those reported in the hands, with type II afferents displaying the largest receptive fields in both regions. Receptive field characteristics are thought to reflect class specific mechanoreceptor morphology and termination depths. It is important to note that the 4-5 times threshold method of calculating receptive fields in the hands and feet is arbitrary, however it is a consistent method that has been used to quantify activation areas across body regions and afferent classes.

Receptive field distribution

The distribution of cutaneous afferents across the foot sole could indicate areas of relative tactile importance (concentration of afferents). In the hand, the high concentration of type I afferents in the finger tips relative to the palm is thought to reflect the functional significance of tactile feedback from the fingers (Johansson and Vallbo, 1979b). To analyze the cutaneous afferent distribution in the foot sole, we began with a χ^2 test across nine-foot sole regions (Figure 2). Based on the relative size of each plantar skin region, this test indicated that the observed proportion of units in each area was highly non-uniformly distributed ($\chi^2 = 31.999$, $p < 0.001$). We calculated the likelihood ratio of randomly sampling a cutaneous receptor in general, and for each class by dividing the proportion of the total units sampled in each region by the proportion of the total foot sole area for each region (Table 3). Following Johansson & Vallbo (1979), we used binomial tests to examine pairwise differences between different plantar skin regions. The hypothesis tested by these binomial tests is given by the equation,

$$P_A = \frac{a}{a + b}$$

where P_A is the proportion of units sampled from region A of the total number of units sampled from regions A and B, and a and b are the areas of the two corresponding skin regions. Previous work reports an even distribution of cutaneous afferents across the foot sole (Kennedy and Inglis, 2002), however the present data demonstrates regional variation. Notably, the present data reveal a higher proportion of cutaneous afferents to innervate the toes (digits 2-5), as well as LatMet, and LatArch than expected if an even distribution was present (Table 3). To simplify the interpretation of this analysis, we chose to perform pairwise binomial tests for three distinct comparisons; proximal-distal over the whole foot sole, and medial to lateral for two regions, metatarsal and arch (see Figure 6).

To investigate the potential for any proximal-distal distribution gradient we compared the toes (collapsing over GT and digits 2-5), metatarsals/arch (collapsing over medial, middle, and lateral portions), and the heel. For all units, binomial tests revealed that the toes had significantly more sampled afferents than the metatarsals/arch ($p < 0.001$), and heel ($p < 0.001$), and the metatarsals/arch had significantly more sampled afferents than the heel ($p = 0.013$) (see Figure 6A). For FAI afferents, binomial tests revealed that the toes had significantly more sampled afferents than the metatarsals/arch ($p < 0.001$), and heel ($p < 0.001$), and the metatarsals/arch had significantly more sampled afferents than the heel ($p = 0.014$); for SAI afferents, binomial tests revealed that the toes had significantly more sampled afferents than the metatarsals/arch ($p < 0.001$), and heel ($p < 0.001$) (Figure 6A). For type II afferents (FAII and SAII), there were no significant differences in afferent distribution across the three skin regions. Thus, we observed that the distribution of foot sole cutaneous afferents increases from the heel to the toes, driven primarily by type I afferents, with little evidence of a gradient for FAII and SAII afferents. This mirrors previous observations for the hand, where an abrupt increase in type I afferent density is observed in the fingertips compared to the middle phalanges and the palm (Johansson and Vallbo, 1979a).

We additionally investigated the potential for a medial-lateral sampled distribution gradient. To accomplish this, we compared the medial, middle, and lateral portions of both the metatarsals, and the arch. In the metatarsals, for all units, binomial tests revealed that the lateral portion had a significantly greater number of sampled afferents than middle ($p = 0.013$), and medial ($p = 0.002$) portions (see Figure 6B). For FAI afferents, binomial tests revealed that the lateral portion of the metatarsals had significantly more sampled afferents than the medial portion ($p = 0.007$); SAI, FAII, and SAII afferents were uniformly distributed across the metatarsals ($p > 0.05$) (Figure 6B). Similarly, in the arch, for all units, binomial tests revealed that the lateral portion had significantly more sampled afferents than the middle ($p < 0.001$), and medial ($p < 0.001$) portions (see Figure 6C). For FAI afferents, binomial tests revealed that the lateral portion of the arch had significantly more sampled afferents than the middle ($p < 0.001$), and medial portion ($p = 0.001$); similarly, for SAI afferents, binomial tests revealed that the lateral portion of the arch had significantly more sampled afferents than the middle (p

= 0.011), and medial portion ($p = 0.014$), and FAII and SAII afferents were uniformly distributed across the arches ($p > 0.05$) (Figure 6C). These observations support the presence of a medial to lateral distribution gradient across both the metatarsals and arch, with a greater proportion of receptors residing in more lateral regions. A similar medial-lateral afferent distribution gradient is not observed in median nerve recordings of hand cutaneous afferents (Johansson and Vallbo, 1979a).

The proximal-distal and medial-lateral distribution gradients of type I cutaneous afferents across the foot sole has not been reported previously. The smaller sample of cutaneous afferents analysed by Kennedy & Inglis 2002, revealed an even distribution of cutaneous afferents across the foot sole. The present larger data set demonstrates that the foot sole displays regions of relatively high (toes, lateral border) and low (heel and medial border) afferent innervation; which is similar to the density gradients in the proximal-distal increase of cutaneous afferent innervation long understood in the hand (Johansson and Vallbo, 1979a). The functional implication of these afferent distribution gradients is discussed below.

Innervation density

The density of mechanoreceptor afferents in the skin influences tactile sensitivity (ability to detect small changes in stimulus amplitude) and acuity (ability to distinguish spatially distributed points on the skin surface). To provide estimates of the innervation density of the four afferent classes for each plantar skin region, we derived a scaling factor based on the approximate total number of cutaneous afferents in the plantar nerves. To obtain this scaling factor, we divided the estimated total number of cutaneous afferents (1,702 units) by the total number of sampled units (364 units), giving the value 4.676. By multiplying this scaling factor by the sampled densities (i.e., the number of units sampled divided by the size of the skin region), we arrive at estimates for the absolute innervation density in each region. The estimated total innervation densities, as well as the innervation densities of the four different receptor classes are presented in Figure 6 and listed in Table 3. In accordance with the distribution results, the highest innervation density was in the toes (23.3 units/cm^2), followed by the lateral arch (15.4 units/cm^2), and the lateral metatarsals (11.2 units/cm^2). The lowest innervation density was in the medial metatarsals (4.9 units/cm^2). Type I afferents most densely innervate the toes (FAI: 12.2 units/cm^2; SAI: 6.9 units/cm^2), followed by the lateral arch (FAI: 8.7 units/cm^2; SAI: 2.8 units/cm^2), and the lateral metatarsals (FAI: 5.6 units/cm^2; SAI: 1.6 units/cm^2). FAII afferents most densely innervate the lateral arch (1.5 units/cm^2), followed by the great toe (1.4 units/cm^2), and the middle metatarsals (1.4 units/cm^2). SAII afferents most densely innervate the lateral metatarsals (3.3 units/cm^2), followed by the toes (2.8 units/cm^2), and the lateral arch (2.4 units/cm^2).

Functional interpretation: A role in standing balance and gait

The control of balance, whether in standing or during gait is a complex sensorimotor task that is facilitated by the integration of sensory feedback from multiple sources including the vestibular, visual and somatosensory systems (Horak et al., 1990; Winter, 1995; Thomas et al., 2003). Although it is difficult to equate behavior at a systems level to the firing of individual neurons, it is through neuronal interactions that functional outcomes emerge. There is mounting evidence that plantar cutaneous input is crucial for the control of standing balance and gait (Kavounoudias et al., 1998; Nurse and Nigg, 1999; Meyer et al., 2004a; Zehr et al., 2014). Evidence suggests that standing posture is sensed in part by the tactile and pressure feedback transmitted by cutaneous afferents in the feet. The functional importance of this feedback has been highlighted through different experimental designs; including the experimental reduction (Perry et al., 2000; Eils et al., 2004; McKeon and Hertel, 2007; Howe et al., 2015) or enhancement (Kavounoudias et al., 1999; Priplata et al., 2006; Perry et al., 2008; Lipsitz et al., 2015) of skin feedback, as well as through the study of naturally reduced cutaneous feedback that can occur with age (Perry, 2006; Peters et al., 2016) and disease (Deshpande et al., 2008; Patel et al., 2009). In cases where foot sole cutaneous feedback is reduced, measures of balance and gait performance are altered (Nurse and Nigg, 1999; Perry et al., 2000; Meyer et al., 2004a). Conversely, measures of standing balance and gait performance have been improved through different interventions that increase foot sole cutaneous feedback (Priplata et al., 2006; Perry et al., 2008; Lipsitz et al., 2015). Together these studies support a role of cutaneous feedback in the control of balance and gait; however more work is necessary in order to link neural firing to balance control.

In both standing balance and gait, posture is controlled through the manipulation of the center of mass (COM) location relative to the base of support (BOS) (Winter, 1995). In other words, if our body mass falls forward or backward, we need cues that will tell us to step as we have lost our balance. For bipeds, the soles of the feet are the only interface with the ground. Forces from the ground on the foot, and foot on the ground are perceived through the foot sole skin and are manipulated to control body equilibrium and orientation. In healthy people, small adjustments of ankle torque are sufficient to control the COM body position during standing balance. This *ankle-strategy* however may not work in populations where tactile feedback is impaired, such as older adults (Manchester et al., 1989; Perry, 2006; Peters et al., 2016) because the feedback from the foot sole is not sufficient to give cues as to how far forward or backward the body is leaning. Indeed, it has been suggested that the CNS uses cutaneous feedback from the soles of the feet to deduce body orientation (verticality) and to help control the forces applied by the feet to manipulate the body COM (Kavounoudias et al., 1998; Meyer et al., 2004b). Although cutaneous afferent firing has not been measured during standing balance, we speculate that foot sole cutaneous afferent firing corresponds to foot sole ground reaction forces and provides feedback about the movement and position of the COM over the feet.

Our findings on the distribution and density of foot sole cutaneous afferents presented in this review contributes new information about how these receptors might modulate balance outcomes. With high receptor populations in the toes and lateral border of the foot, these regions are identified as important sensory locations with populations able to delineate the physical limits of the BOS and evoke appropriate postural responses. The toes dictate the anterior limit of the BOS. Through plantar and dorsiflexor muscles activation we can control the posterior and anterior movement of the COM within the confines of the BOS, which is identified by these toe mechanoreceptors. Naturally we stand with our COM further toward the front of our foot lever (Winter, 1995), specifically over 60% of the load during stance is applied to the metatarsals and toes (Fernández-Seguín et al., 2014) supporting the need for a density of receptors in the toes to define the contact limits. Similarly, the heel provides the initial contact site during gait and dictates the posterior boundary of the BOS; however, unlike the toes, the heel is not a segment that can be independently manipulated to control the COM. The increased distribution of cutaneous afferents in the toes compared to the heel may reflect the postural significance of feedback from the toes in the control of standing balance. In the frontal plane, the lateral border of the right and left feet defines the boundary of the BOS. If the COM moves beyond the lateral BOS, a stepping reaction is required to prevent a fall (McIlroy and Maki, 1996). In contrast, a medial movement of the COM is relatively less threatening to balance due to the support of two legs. FAI afferents have been shown to have strong synaptic coupling to lower limb motor neurons (Fallon et al., 2005), and the relatively large population of FAI afferents in the toes and lateral foot sole border may help facilitate reflexive loops important in balance control. In fact, increasing cutaneous feedback from the foot sole border has been shown to increase the COM-lateral BOS stability margin in older adults (Perry et al., 2008). Furthermore, activation of location specific skin regions on the sole of the foot has been shown to modulate muscles of the lower limb to facilitate gait (Zehr et al., 2014). This very direct evidence supports the notion that the individual mechanoreceptors have a significant role in spinal reflexes to control the magnitude of muscle activation for successful ambulation. With pressure distribution across the foot during walking that travels from heel to the great toe, while favouring greater pressure on the lateral border (Buldt et al., 2018) the density and distribution of receptors in these regions makes inherent sense for this dynamic control of movement.

Future considerations

Collectively, the studies and data highlighted in this review enhance the understanding of foot sole cutaneous afferent firing thresholds and receptive field distribution and density, that together help shape how the foot sole is viewed as a sensory structure. Continued investigations into the foot sole skin is needed to understand the contribution of class specific and integrated foot sole cutaneous feedback in balance control. Some directions for future steps include the histological study of cutaneous afferent innervation of the foot sole and structure of the mechanoreceptor endings. How do they compare to hand mechanoreceptors? Measurements of the number of Aβ fibres innervating the foot sole would provide more accurate estimates of the mechanoreceptor innervation density. How accurate is the estimated innervation ratio of 10 times fewer foot sole afferents compared to the hand? Foot sole mechanoreceptor morphology may adapt in response to the larger forces associated with standing balance and gait. Understanding how foot sole cutaneous afferents respond under loaded conditions is critical to assign functionality to cutaneous feedback in postural control. Vibration perception thresholds have recently been shown to be elevated in a standing compared to sitting posture (Mildren et al., 2016), however the behaviour of the underlying mechanoreceptors in different loading conditions is unknown. Therefore, future work is needed to investigate firing characteristics of foot sole afferents under loaded, and more functionally relevant conditions.

Summary and conclusions

The foot sole is a critical sensory structure, often our only contact with the environment during upright stance. In this review, we combined datasets with unpublished recordings to provide a collated and detailed view of the cutaneous innervation of the foot sole. By combining data sets we are able to highlight significant functional differences in the skin of the foot, as compared to the hand. Our principal novel finding was the observation that there is unequal distribution of afferents across the foot sole. Similar to the hand (Johansson and Vallbo, 1980), a proximal (heel) to distal (toes) increase in afferent density was found. In addition, the data supports a higher density of afferents on the lateral border of the foot sole compared to the midline or medial border. Afferent firing thresholds did not show the same proximal-distal or medial-lateral distribution pattern, although the heel was the least sensitive location as well as being the least densely populated area. It is well established that in situations where cutaneous feedback is impaired experimentally (Meyer et al., 2004b) or naturally with age (Peters et al., 2016) and disease (Prätorius et al., 2003) balance impairment are prevalent (Kars et al., 2009). Advances have been made in the development of sensory augmentation devices as a strategy to improve standing balance. These developmental intervention strategies have attempted to improve the quality of foot sole cutaneous feedback through specialized shoe insoles (Perry et al., 2008; Lipsitz et al., 2015). However, optimizing these interventions requires an understanding of the underlying cutaneous mechanoreceptor afferents; notably their capacity to provide functionally relevant feedback (Parker and Newsome, 1998). The toes and lateral boards of the feet are important regions for balance control as they delineate the borders of the base of support. The observed afferent distribution and firing thresholds are thought to reflect the functional role of the foot sole, where tactile feedback from the toes and lateral border may be more meaningful for the control of standing balance. These data significantly advance how the foot sole is viewed as a sensory structure, however future work is needed to investigate the firing characteristics of cutaneous afferents under loaded and more natural conditions.

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Figure captions:

Figure 1. An illustration of the human microneurography technique. (**A**) *Top*: Schematic of experimental setup for recording from the tibial nerve at the level of the knee (popliteal fossa). Two tungsten microelectrodes are inserted percutaneously with one serving as the reference electrode inserted beneath the skin near the nerve, and the other serving as the active electrode which gets inserted into the nerve. *Bottom*: Schematic of a peripheral nerve, showing the active electrode's placement into an individual nerve fascicle, right up next to a single axon (i.e., intrafascicular extracellular recording). (**B**) Sample recording from an FAI afferent showing, from top to bottom, the instantaneous firing rate, raster plot, raw neurogram, and vibrator acceleration for the case of 30 and 250 Hz vibration. As expected based on the FAI bandwidth, this unit codes precisely for the 30 Hz vibration with a phase-locked 30 Hz spike train but fails to be activated by the 250 Hz stimulation. *Inset left:* sample of phase-locking in the FAI response with the time scale expanded. *Inset right:* 100 overlaid spikes (Note: the double-peaked action potential morphology indicates that the microelectrode has not caused conduction blockage; see (Inglis et al., 1996).

Figure 2. Receptive fields of the different cutaneous mechanoreceptor classes. *Top:* Foot sole maps for each afferent type showing all the receptive field locations and estimate of size in the present data set. Grey ellipses represent individual afferent receptive fields. *Bottom:* Composite foot sole map showing the center of all receptive fields overlaid on the same foot template. Additionally, a pie chart depicts the breakdown in terms of the percentages of each afferent type in the present data set.

Figure 3. Foot sole area measurement. We measured the surface areas of 9 different individual regions on the foot soles of 4 men and 4 women. On the left is the largest foot we encountered (male, age 25, U.S. men's size 12 shoe), and on the right is the smallest (female, age 25, U.S. women's size 6 shoe). The skin regions were traced from an optical scan of each individual's right foot sole (light green outlines), and digital area measurements were made using ImageJ software.

Figure 4. Mechanical thresholds for the different cutaneous mechanoreceptor classes. The mean (SE) threshold for evoking an action potential in the 9 different skin regions are given for all afferent types (**A**), FAI afferents (**B**), FAII afferents (**C**), SAI afferents (**D**), and SAII afferents (**E**).

Figure 5. Receptive field sizes for the different cutaneous mechanoreceptor classes. The mean (SE) area of receptive fields in the 9 different skin regions are given for all afferent types (**A**), FAI afferents (**B**), FAII afferents (**C**), SAI afferents (**D**), and SAII afferents (**E**).

Figure 6. Estimates of the relative and absolute density for the different cutaneous mechanoreceptor classes across the foot sole. (**A**) Depiction of the proximal-distal gradient in receptive field density, with greater innervation density in the toes (red), than in the metatarsals/arch (orange), and heel (yellow). (**B**) Depiction of the medial-lateral

gradient in receptive field density across the metatarsals, with greater innervation density in the lateral region (red), than in the middle (orange), and medial (yellow) regions. (**C**) Depiction of the medial-lateral gradient in receptive field density across the arch, with greater innervation density in the lateral region (red), than in the middle (orange), and medial (yellow) regions.

Table captions:

Table 1: The cutaneous afferent contribution from published and unpublished sources making up the present data set

Table 2: The number and percent of foot sole cutaneous afferent class monofilament firing thresholds and receptive field areas (mean, median, and range)

Table 3: The distribution and innervation density estimate of cutaneous afferents across the foot sole