REVIEW | *Biology of Neuroengineering Interfaces*

The biology of skin wetness perception and its implications in manual function and for reproducing complex somatosensory signals in neuroprosthetics

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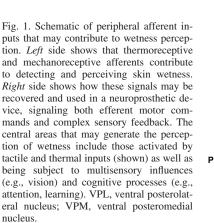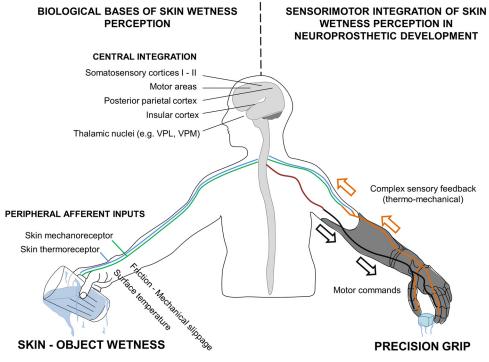
Filingeri D, Ackerley R. The biology of skin wetness perception and its implications in manual function and for reproducing complex somatosensory signals in neuroprosthetics. *J Neurophysiol* 117: 1761–1775, 2017. First published January 25, 2017; doi:10.1152/jn.00883.2016.—Our perception of skin wetness is generated readily, yet humans have no known receptor (hygroreceptor) to signal this directly. It is easy to imagine the sensation of water running over our hands or the feel of rain on our skin. The synthetic sensation of wetness is thought to be produced from a combination of specific skin thermal and tactile inputs, registered through thermoreceptors and mechanoreceptors, respectively. The present review explores how thermal and tactile afference from the periphery can generate the percept of wetness centrally. We propose that the main signals include information about skin cooling, signaled primarily by thinly myelinated thermoreceptors, and rapid changes in touch, through fast-conducting, myelinated mechanoreceptors. Potential central sites for integration of these signals, and thus the perception of skin wetness, include the primary and secondary somatosensory cortices and the insula cortex. The interactions underlying these processes can also be modeled to aid in understanding and engineering the mechanisms. Furthermore, we discuss the role that sensing wetness could play in precision grip and the dexterous manipulation of objects. We expand on these lines of inquiry to the application of the knowledge in designing and creating skin sensory feedback in prosthetics. The addition of real-time, complex sensory signals would mark a significant advance in the use and incorporation of prosthetic body parts for amputees in everyday life.

wet; prosthetics; sensation; touch; temperature

MERELY THINKING OF GRIPPING a cold, wet bottle of water, walking on a warm, humid summer afternoon, washing the dishes, or taking a shower is sufficient to evoke the memory of the unmistakable sensory experience that accompanies human life, from its intrauterine commencement: the perception of skin wetness. Although the question of what mechanisms contribute to our ability to sense the presence of moisture on the skin was first tackled over 100 years ago (Bentley 1900), the neural substrates of this sensory process have only recently started to be investigated. Studies have shown the importance of tactile

and thermal afference in signaling wetness; however, there is no evidence that humans possess a specific sensory receptor for the transduction of skin wetness into neural signals, that is, a putative human hygroreceptor. The combination of mechano- and thermoreceptive inputs readily leads to our perception of skin wetness, and these inputs are relevant to performing such tasks as precision grip, object manipulation, and sensing slippage (e.g., when a wet glass starts to fall from our hand; see Fig. 1). The accurate sensing of physical wetness means we can rapidly assess an external event and produce appropriate actions (e.g., changing our grip on a wet glass to prevent it from falling). Accurate sensorimotor actions are made difficult through the loss of a body part; current prostheses provide some recovery of movements but do not provide essential

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Fig. 1. Schematic of peripheral afferent inputs that may contribute to wetness perception. *Left* side shows that thermoreceptive and mechanoreceptive afferents contribute to detecting and perceiving skin wetness. *Right* side shows how these signals may be recovered and used in a neuroprosthetic device, signaling both efferent motor commands and complex sensory feedback. The central areas that may generate the perception of wetness include those activated by tactile and thermal inputs (shown) as well as being subject to multisensory influences (e.g., vision) and cognitive processes (e.g., attention, learning). VPL, ventral posterolateral nucleus; VPM, ventral posteromedial nucleus.

sensory feedback. The present review focuses on the biological basis of wetness perception and its potential implications for manipulative actions, including the addition of such signals in future neuroprostheses.

Biological Bases of Skin Wetness Perception

Since the classic work of Muller on the "law of specific nerve energies" (cited in Norrsell et al. 1999), the first step in exploring the biological mechanisms behind the function of a sensory system has often been the search for the specific receptor responsible for transducing a physical stimulus into a neural signal. Mechanoreceptive, nociceptive, and thermoreceptive nerve endings in the skin have been identified anatomically and characterized physiologically as the biological transducers of touch, pain, and temperature, respectively (Lumpkin and Caterina 2007). To date, no hygroreceptor has been found in human skin for sensing wetness (Clark and Edholm 1985), although it is important to remark that the search for such a biological structure has never been formally undertaken in humans. This is in contrast with information available on the presence and function of hygroreceptors in other species (Filingeri 2015; Kim and Wang 2016). Humidity-sensitive sensory organs are present in numerous insects, including fruit flies and cockroaches, and the investigation of their neural and molecular substrates is currently receiving significant attention (Enjin et al. 2016; Kim and Wang 2016; Liu et al. 2007; Russell et al. 2014; Tichy and Kallina 2010).

In humans, skin wetness has been found to be a distinct perceptive property of the tactile experience, which is separable from other tactile (e.g., texture) and temperature (e.g., heat, cold) facets (Ackerley et al. 2014c). However, until a putative human hygroreceptor is ever identified, we must consider alternative mechanisms for the sensory integration of skin wetness perception in humans. The analysis of the physical, biophysical, and neurophysiological processes occurring during the interaction of moisture with the skin highlights the

candidate somatosensory inputs that are likely to play a prominent role in decoding wetness. Physically, the interaction of moisture with the skin involves both a thermal and a mechanical component. The conductive and evaporative heat transfer occurring when moisture contacts the skin determines the thermal component. The skin deformations induced by the mechanical interaction between skin and moisture determines the mechanical component. Biophysically, these thermal and mechanical interactions govern changes in skin temperature and in skin mechanics. Neurophysiologically, these cutaneous stimuli trigger the activation of temperature- and mechanosensitive neurons innervating the skin (i.e., thermoreceptors and mechanoreceptors) (Table 1). On this basis, it can be hypothesized that thermal and mechanical (tactile) afferent inputs are the most probable somatosensory cues used by humans to sense skin wetness (Filingeri and Havenith 2015).

Peripheral temperature afferent input. Humans readily distinguish between different levels of skin wetness with discrimination thresholds as little as 0.04 ml (Ackerley et al. 2012b; Sweeney and Branson 1990). How can we present such remarkable wetness sensitivity in the absence of a specific skin hygroreceptor? The available psychophysical data on wetness perception point to the significant role that thermal cues play in decoding skin wetness. It would indeed appear that evaporation-induced skin cooling and nonnoxious cold sensations underpin our skin wetness sensitivity. Specifically, individuals seem to use the level of skin cooling and coldness experienced when in contact with moisture as an indicator of the level of skin wetness (Ackerley et al. 2012b; Filingeri et al. 2013, 2014a). Supporting this hypothesis is the observation that wetter perceptions are often associated with colder sensations (Bergmann Tiest et al. 2012a). The dependency of skin wetness perception on thermal, and particularly cold, sensory inputs has been clearly shown when an illusion of wetness could be induced in blindfolded naive individuals exposed to nonnoxious cold-dry stimuli inducing skin cooling (range: 0.14–

Table 1. *Overview of the proposed afferents involved in the perception of wetness in humans*

Afferent Type	Signals	Axon	Cutaneous Region	Receptor	Details
Aδ-cool	Temperature	Thinly myelinated	All skin*	Free nerve ending	Thought to be the main afferents in signaling conscious, cold-wet information
C-cold	Temperature	Unmyelinated	All skin*	Free nerve ending	May play a role, if more subconscious, in signaling cold-wet interactions
C-warm	Temperature	Unmyelinated	All skin*	Free nerve ending	Signals innocuous warm-wet interactions
Fast-adapting type 1	Touch	Myelinated	Glabrous skin	Meissner corpuscles	Signals conscious aspects of tactile interactions, typically from the hands, including texture and stickiness
Fast-adapting type 2	Touch	Myelinated	All skin	Pacinian corpuscles	Signals vibrations well and may contribute to the detection of low-force wetness interactions (e.g., sensing fine drops of rain)
Slowly adapting type 1	Touch	Myelinated	All skin	Merkel endings	Signals conscious aspects of tactile interactions and may be well-suited for stickiness/slippery encoding
Slowly adapting type 2	Touch	Myelinated	All skin	Ruffini endings	Usually considered to signal higher force tactile interactions in glabrous skin, but may signal minimal-force wetness interactions in hairy skin
Field	Touch	Myelinated	Hairy skin	Unknown	Very sensitive touch afferents that likely signal minimal force wetness interactions in hairy skin
Hair	Touch	Myelinated, thinly myelinated	Hairy skin	Hairs	Signals hair movements, from both terminal (thick) and down (fine) hairs; hairs signal wetness interactions well, although the signal may change if the hairs are saturated
C-tactile (CT)	Touch	Unmyelinated	Hairy skin	Free nerve ending	May signal more subconscious and affective aspects of gentle touch

Regarding the axon, myelinated axons are fast-conducting (>30 m/s) and unmyelinated axons are slow-conducting (<2 m/s), whereas the Aδ-cool thinly myelinated axons conduct signals relatively slowly at ~3–8 m/s. See text for further details. *The innervation of thermal afferents in human glabrous skin is unknown from microneurography and is usually inferred from psychophysical tests and animal work. This is due to the rarity of recording from thermoreceptive afferents, especially in glabrous skin, which may or may not be related to their relative density. Results from warm and cold sensation thresholds have produced estimates of conduction velocities of 1.6 and 2.6 m/s, respectively, in glabrous skin (Yarnitsky and Ochoa 1991), which means that C-warm fibers likely exist in glabrous skin, but it is inconclusive whether cold sensation comes from very thinly myelinated Aδ-fibers or C-fibers, or more likely both. Studies from the radial nerve (supplying the dorsal hairy skin of the hand, but also glabrous-border skin) and monkey studies have shown general agreement in that cold sensations in glabrous skin are signaled by both Aδ- and C-fibers (Konietzny 1984). However, temperature sensitivity differs over the body (e.g., distal-proximal; also cf. nociception from Aδ- and C-fibers; Towell et al. 1996), and the exact skin type (e.g., thickness of glabrous skin) will affect both the encoding and transmission of temperature signals on the skin.

0.41°C/s) and cold sensations (Filingeri et al. 2013, 2014c) comparable to the ones occurring under actual contact with moisture (Daanen 2009; Filingeri 2014). With the use of similar levels of dry skin cooling, it also has been shown that wetness perceptions could be induced on different skin regions across the human torso, with varying magnitude depending on the regional patterns of cold sensitivity (i.e., regions more sensitive to cold seem also more sensitive to wetness; Filingeri et al. 2014b).

From a neurophysiological point of view, two classes of cutaneous fiber populations are responsible for the coding of the cooling component of wetness (i.e., Aδ- and C-fibers) (Table 1). In humans, thinly myelinated Aδ-fibers are selectively sensitive to nonnoxious skin cooling in the range of 30°C to 14°C (Campero et al. 2009; Hensel and Boman 1960), with a conduction velocity of ~3–8 m/s (Campero and Bostock 2010). They innervate the skin densely (1–19 spots per cm², <1-mm receptive field), where the palm has the lowest innervation, and the lips the highest (Hensel 1981). Cold-sensitive Aδ-fibers present a steady-state thermal sensitivity that follows a bell-shaped function with a maximum discharge at temperatures around 27°C (Hensel and Boman 1960; in monkeys: Darian-Smith et al. 1973). In light of their specific thermal sensitivity to nonnoxious skin cooling, thinly myelinated Aδ-fibers are generally considered the main neuronal population subserving nonnoxious cold integration (Filingeri 2016) and

are therefore likely to play a primary role in encoding the thermal aspects of skin wetness perception (i.e., evaporative and conductive skin cooling).

Slowly conducting (~1 m/s), unmyelinated C-cold thermoreceptors ("type 2," C2 fibers) discharge steadily at normal skin temperature (~30°C) and are exquisitely sensitive to small changes in decreasing skin temperature from 29°C, although they are insensitive to mechanical stimulation (Campero et al. 2001). These fibers fire maximally at 15–20°C but can encode decreasing temperature to 5°C (Campero et al. 2001). In light of their sensitivity to the type of skin cooling known to induce a perception of skin wetness, these fibers may contribute to encoding wetness on the skin, although they have been proposed to also play a role in thermoregulatory functions (Campero and Bostock 2010).

It is important to highlight that, whereas the thermal component of sensing wetness is primarily related to skin cooling, humans also experience interactions of wetness that are at or above skin temperature (e.g., at the onset of sweating, when bleeding). Accordingly, it cannot be excluded that warm-sensitive fibers may also encode wetness-related interactions. Slowly conducting (~1 m/s), unmyelinated C-warm fibers are selectively sensitive to nonnoxious skin warming in the range of 30–45°C (Konietzny and Hensel 1975) and are considered the only neuronal population subserving peripheral nonnoxious warm integration (Darian-Smith 2011). They innervate the skin

less densely (up to 1.7 per cm^2) than cold thermoreceptors, where the chest has the lowest density, and the face and fingers the highest (Hensel 1981). These fibers may therefore encode interactions of wetness that are at or above skin temperature, although due to the primary involvement of cooling in wetness perception, these afferents are likely to play secondary role than their cold- and mechanosensitive counterparts (Filingeri et al. 2014a).

The cold and warm thermoreceptors likely involved in wetness sensing are particularly sensitive to dynamic changes in skin temperature (e.g., when a drop of rain first contacts the skin or when water evaporates from it). Thermoreceptive fibers show an initial overshoot, followed by a progressive decrease in their discharge frequency, on sudden changes in skin temperature (Darian-Smith et al. 1973, 1979; Johnson et al. 1979). The decrease in initial discharge frequency usually accompanies the end of a dynamic change in skin temperature and persists at steady-state cold or warm skin temperatures. This profile underlies psychophysical phenomena such as thermal adaption, where the initial thermal sensation experienced on sudden cooling or warming decreases in intensity with time (Kenshalo and Scott 1966). Neurophysiological studies in primates have indicated that the magnitude, as well as the rate of change, of skin temperature determines both peak discharge frequency and cumulative impulses over time in thermoreceptors (Darian-Smith et al. 1973, 1979; Johnson et al. 1979). Higher peak discharge frequency correlates with more intense sensations, and the cumulative impulses determine the timing and duration at which the thermal sensation is experienced at its maximal intensity (Filingeri 2016).

Under real-life conditions, thermal stimulation of the skin results in the activation of a population of thermoreceptive fibers, whose number depends on the areal extent of stimulation. Evidence indicates that the primate central nervous system likely averages, or optimally integrates, responses from populations of fibers to code stimulus intensity and to ensure the maximal transmission of information (Johnson et al. 1979). Under optimal peripheral integration, it appears that as few as 15 concurrently engaged fibers are sufficient to explain human thermosensory performance (Johnson et al. 1979).

Population coding and local thermosensitivity of skin areas vary across the body, and extensive evidence exists on regional differences in thermosensitivity (Burke and Mekjavić 1991; Filingeri et al. 2014b; Gerrett et al. 2015; Nakamura et al. 2008; Ouzzahra et al. 2012; Stevens et al. 1974). Differences in the density of thermally receptive fields on the skin, as well as in the central integration and weighting of peripheral thermal inputs, seem to play a role in the observed regional variation in thermal sensitivity across the human body. Body regions such as the face are significantly more sensitive to warmth than the torso and the limbs (Gerrett et al. 2014). On the contrary, cold sensitivity appears to be higher on the torso (particularly the abdomen) than on the head and limbs (Stevens 1979). Topographical variations in thermal sensitivity also occur within individual skin regions, such as the palm of the hand (Li et al. 2008). Furthermore, regional variations in wetness sensitivity have been reported in heathy individuals (Ackerley et al. 2012b; Filingeri et al. 2014b), and these correlate well with the pattern of cold sensitivity across the same body regions (Filingeri et al. 2014b).

The complexity in the peripheral coding of temperature highlights the challenge of reproducing intact human thermosensory performance that is essential for accurate wetness sensing, especially in engineering sensory neuroprostheses. The development of interconnected thermal sensors to provide accurate and realistic thermosensory feedback for wetness sensing is required for conveying a wide range of nonnoxious temperatures. These sensors should be assembled according to known patterns of regional thermal and wetness sensitivity, because this arrangement and the accuracy in thermal sensing underlie the implementation of a synthetic perception of skin wetness within neuroprostheses.

In summary, peripheral nonnoxious thermal inputs triggered by decreasing skin temperature readily signal the presence of skin wetness (Filingeri and Havenith 2015), and applied stimuli that are warmer than the skin appear to suppress the perception of wetness (Filingeri et al. 2015b). That does not mean that warm water interactions do not feel wet; rather, it is likely that tactile signals may contribute more to wetness perception in the absence of skin cooling (Filingeri et al. 2015a), along with other sensory cues (Bergmann Tiest et al. 2012b), such as visual inputs (Bergmann Tiest 2015).

Peripheral tactile afferent input. A clear role for decreasing skin temperature has been shown in the perception of skin wetness, yet touch very often plays a critical role (Bentley 1900; Bergmann Tiest et al. 2012b; Filingeri et al. 2015a). In its purest form, the perception of wetness is formed when the skin comes into contact with water, such as when the hands are immersed in a bath of water. This example shows the complexity of wetness sensing and demonstrates the tactile component well; bath water is often slightly warmer than skin temperature, yet we are well aware that our hand feels wet. This is, in part, also signaled from visual cues and the behavioral event, but we nevertheless feel a contact component, both as our skin is submerged in the water and when our hand is moving through the water. The critical role of mechanoreceptors in sensing wetness is highlighted by Bentley (1900), where participants dipped a sheath-covered finger into a liquid and the participants at first refused to believe that the finger was not actually wet. Since then, studies have investigated the contribution of tactile input to detecting experiences such as the related experiences of slip and stick, yet few have truly explored wetness.

The importance of mechanical interactions between skin and moisture is evident under conditions of contact with external wet stimuli, as well as during active sweating (Filingeri et al. 2015a). The manipulation of tactile cues, in the form of increasing or decreasing the level of mechanical stimulation of the skin, significantly alters skin wetness perception, independently of the level or presence of moisture on the skin. For example, during contact with sweat or wet stimuli, higher mechanical pressure on the skin, such as that resulting from the wearing of tight-fitting clothing (Filingeri et al. 2015a), significantly reduces the perception of skin wetness. On the contrary, dynamic interactions between skin and moisture, such as that occurring during haptic exploration of a wet stimulus (e.g., a moist textile; Bergmann Tiest et al. 2012b; Bergmann Tiest 2015), significantly increase wetness sensitivity.

In humans, specialized mechanoreceptors in the skin transduce specific qualities of external touch interactions, delivering a wealth of tactile information to the central nervous system

(Table 1). Mechanoreceptive afferents can be subdivided by a number of criteria, such as whether the afferent is fast-adapting on contact with a surface or slowly adapting (i.e., it keeps firing to sustained pressure), and by differences in the afferent skin innervation (e.g., glabrous or hairy skin) (for reviews see Ackerley and Kavounoudias 2015; Johnson 2001; Vallbo and Johansson 1984). The low-threshold, fast-conducting, myelinated $A\beta$ mechanoreceptive afferents in glabrous, nonhairy skin (e.g., the palm) comprise fast-adapting type 1 (FA1; Meissner) and type 2 (FA2; Pacinian) afferents, and slowly adapting type 1 (SA1; Merkel) and type 2 (SA2; Ruffini) afferents. In hairy skin, which covers the majority of the body (e.g., the arm), FA1 afferents are not present; however, fast-adapting myelinated hair and field afferents, as well as intermediately adapting, slowly conducting, unmyelinated C-tactile (CT) afferents, are additionally found.

The in vivo technique of microneurography has provided us with unrivalled views into the properties of mechanoreceptive afferents from all over the human body (see Vallbo et al. 2004 for an overview of the technique and its applications). The skin of the hand is renowned for signaling the discriminative aspects of touch, and microneurography studies have shown its importance in detecting edges, pressure, force, and vibration (Johansson and Vallbo 1979a; Knibestöl 1973,; 1975; Knibestöl et al. 1980), as well as more complex facets such as texture and feature detection (Connor et al. 1990; Phillips et al. 1992; Pruszynski and Johansson 2014; Saal et al. 2009; Weber et al. 2013). This enables us to distinguish between a vast range of surfaces and gives precise feedback during object manipulation, which is essential in processes such as precision grip (see *Sensorimotor implications of skin wetness perception for precision grip* for details). However, it is not known which mechanoreceptive afferents encode the exact properties of wetness and other related percepts such as stickiness, dampness, greasiness, and slipperiness.

The potential main mechanoreceptors involved in detecting wetness are the fast-conducting afferents with a low activation threshold that are sensitive to movements on the skin (see Table 1). In glabrous skin, this comprises the FA1, FA2, and SA1 afferents, although SA2s likely also contribute during skin stretch. The FA1 and FA2 afferents most sensitive to touch originate in the hand, where they are typically activated by monofilaments of around 0.5 mN, although this is slightly higher for SA1s (1.3 mN) and much higher for SA2s (7.5 mN) (Johansson et al. 1980). Although the FA1 and FA2 afferents have similar tactile thresholds, their receptive fields differ greatly; FA1s have very small receptive fields (~11 mm^2), whereas those from FA2s are very large (~100 mm^2) (Johansson and Vallbo 1980). FA2s are extremely sensitive to remote vibrations that are transmitted through the skin, demonstrated in the remote detection of a rough stimulus at the hand by FA2s in the arm (Delhaye et al. 2012; Klatzky and Lederman 1999; Libouton et al. 2012; Yoshioka et al. 2007).

The SA1s have a similar receptive field size to the FA1s (~12 mm^2; Johansson and Vallbo 1980) but are distinctly different in that they preferentially encode pressure. Together, these afferents are good candidates to provide different aspects of the tactile experience and likely signal aspects of wetness, e.g., encoding properties of a sticky or greasy surface. These types of stimuli would produce additional activity from the afferents due to prolonged surface contact, compared with a dry surface that would not adhere to the skin. Furthermore, the exquisite vibrational coding capability of FA2s may encode subtle interactions with wetness (for example, drops of water), whereas preliminary investigations have shown that FA1, SA1, and SA2 units show no sensitivity to this (Marshall and Ackerley 2014). Finally, it is of interest to determine how physical changes of the skin due to prolonged wet exposure (e.g., water-induced finger wrinkles) impact tactile afferents and their functioning, although the implications of skin wrinkles for manipulative function are still controversial (Haseleu et al. 2014; Kareklas et al. 2013).

It is well worth exploring touch in hairy skin; there are few studies on hairy skin in humans, yet it covers the majority of the body. In terms of neuroprosthetics, recovering sensation from the glabrous skin of the hand would be a great advantage, but the addition of signals from hairy skin sites would also be useful. As well as contributing tactile feedback, this input may help provide a more whole sense of self, thus making for better integration of the prosthetic. Hairy skin provides poorer tactile discrimination but is nevertheless as sensitive as glabrous skin (Ackerley et al. 2014b), if not more so; for example, you may first feel light rain on your face, but it is more difficult to detect with your glabrous hand. In preliminary work, Marshall and Ackerley (2014) found that in hairy skin, FA2, SA2, hair, and field afferents all respond to drops of water applied to their receptive field (but not SA1 or CT afferents). This demonstrates the acuity of hairy skin in sensing any light stimulus on the skin, or even near it in the case of hair movement by air currents. FA2s and SA1s likely play a similar role in detecting mechanical changes on the skin from water, because these afferents have similar properties in hairy skin (cf. Vallbo et al. 1995); however, SA2 afferents are rather different. SA2s have much lower force activation thresholds in hairy skin (~1.3 mN) and tiny receptive fields (~1 mm^2) (Vallbo et al. 1995) compared with those in glabrous skin, although both share similar physiological firing properties. Hence, these hairy skin SA2s are much more likely to play a role in detecting skin wetness than those in glabrous skin, especially because they are sensitive to thermal changes, particularly cooling (as found in animal work; Burton et al. 1972; Chambers et al. 1972).

Hair, field, and CT afferents are also very sensitive to mechanical stimulation, especially when the stimulus is moving. Hair afferents typically compose one axon connected to ~20 hairs; they are readily activated by a light puff of air (Vallbo et al. 1995) and are not modulated by temperature (Ackerley et al. 2014a). Little is known about field afferents, and they are quite rare in microneurography recordings, yet they have very low thresholds for mechanical activation (~0.1 mN; Vallbo et al. 1995). They have large receptive fields (~80 mm^2), a size similar to that of the hair afferents (~110 mm^2; Vallbo et al. 1995). These two types of myelinated afferent very likely convey mechanical aspects of wetness, due to their sensitivity, and large receptive fields, akin to FA2s. It is also likely that hair afferents will signal wetness differently when saturated with water (Marshall and Ackerley 2014), because this restricts their normal movement in the air. Hence, it is clear that the reproduction of high temporal resolution responses from $A\beta$ afferents is required to truly capture the tactile experience, including sensing wetness interactions.

Central integration for skin wetness perception. The primary hypothesis for human skin wetness sensing is based on the

assumption that in the absence of a putative hygroreceptors, humans have developed a '"hygro-sensory strategy" centered on the integration of peripheral thermal (e.g., cold) and mechanical (e.g., stick/slip) inputs resulting from the skin's contact with moisture (Thunberg 1905), which has recently been shown in nematodes (Russell et al. 2014). We have recently shown not only that the mechanisms underlying wetness sensing during skin-object interactions are modulated by cold and mechanical cues, but also that these are independent of the level of physical wetness (Filingeri et al. 2014a), demonstrating prediction in the strategy. Furthermore, we have observed that wetness sensing increases significantly when cold and mechanical cues combine during a dynamic contact with cold-wet stimuli. Artificially reducing neural transmission within peripheral cold- and mechanosensitive skin afferents also hampers wetness sensitivity (Filingeri et al. 2014a) (Fig. 2). From a central processing perspective, to trigger the specific sensory experience of wetness, the central nervous system has to integrate sensory inputs arising from thermosensory and mechanosensory

sources in a coherent way. Multisensory cutaneous integration therefore appears to be of fundamental importance in the central processing of skin wetness perception (Pannunzi et al. 2015; Parise and Ernst 2016).

To date, no direct human neurophysiological evidence is available on the anatomical site or on the functional properties underlying the central integration of skin wetness perception. Likely cortical candidates include the primary (S1) and secondary (S2) somatosensory cortices and the insula, due to their role in somatosensory processing (Craig et al. 2000; Duclaux et al. 1974; Freund et al. 2010; Greenspan et al. 2008; Hua et al. 2005; Iannetti et al. 2003; Olausson et al. 2005; Veldhuijzen et al. 2010; Weiss et al. 2008), and in addition to these, motor areas and the posterior parietal cortex, due to their role in sensing discriminative touch (Ackerley et al. 2012a; Disbrow et al. 2000; Francis et al. 2000; Ruben et al. 2001; Sanchez-Panchuelo et al. 2012; Sanchez Panchuelo et al. 2016) (Fig. 1).

Intercortical interactions (e.g., somatosensory projections to the cingulate and orbitofrontal cortices; Aziz et al. 2000; Rolls
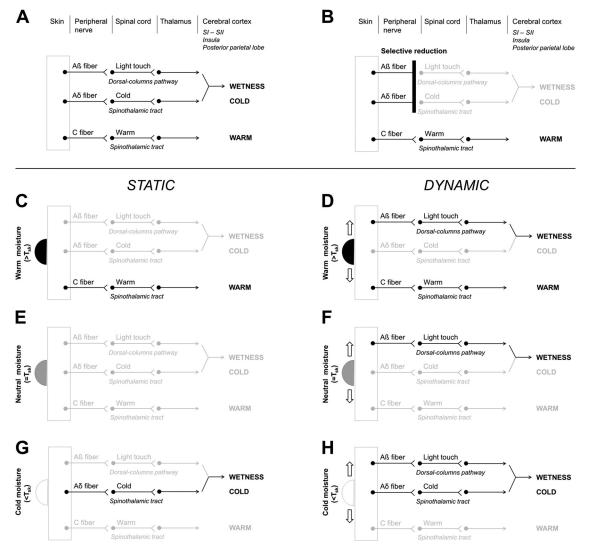

Fig. 2. Neurophysiological model of skin wetness perception. Mechanosensitive (Aβ), cold-sensitive (Aδ), and warm-sensitive (C) peripheral afferents and their projections from the skin to central integration sites are represented. A and B show the neural model of wetness perception (consisting of Aβ and Aδ afferents) under normal function and artificial reduction in the activity of A-nerve fibers, respectively. C, E, and G show the pathways for wetness perception during static contact with warm, neutral, and cold moisture, respectively. D, F, and H show the pathways for wetness perception during dynamic contact with warm, neutral, and cold moisture, respectively. T_{sk}, skin temperature.

2010), as well as interactions with subcortical regions (e.g., solitary nucleus, parabrachial nucleus, hypothalamus; Craig 2011; Damasio et al. 2013), have been suggested to play a role in enriching the polymodal nature of our somatosensory experiences. Perceiving skin wetness represents a prominent example of how multisensory processing is key in producing somatosensory experiences that do not arise from only one specific skin receptor. Input from the other senses, especially vision, plays a role in confirming cutaneous wetness processing, and visual signals have been shown to have a modulatory effect on the S1, for example, having congruent visual signals during a shape identification task (Helbig et al. 2012). Wetness is also readily assessed when one is simply looking at objects and scenes, such as seeing a puddle of water, and the human brain is fully capable of processing these sensory events together, to better process wetness.

Spinal and subcortical structures may play a role in shaping thermal and tactile inputs. Peripheral neural signals travel to the thalamus with high fidelity, where information is largely conserved (Christensen and Perl 1970; Dostrovsky and Craig 1996; Han et al. 1998; Rowe 2002), although there is integration, at least within C-fiber sensory inputs (Craig et al. 2001). In the thalamus, polymodal thermo- and mechanoreceptive neurons exist (Bushnell et al. 1993; Craig et al. 1994; Davis et al. 1998; Martin and Manning 1971) that play a role in the central integration of afferent inputs and in the modulation of sensory filtering to the cortex.

Perceptual frameworks for multisensory integration of visual, tactile, proprioceptive, and auditory inputs are available (Angelaki et al. 2009; Beauchamp 2005; De Gelder and Bertelson 2003; Driver and Spence 2000; Gentile et al. 2011; Kavounoudias et al. 2008; Parise and Ernst 2016). These are effective in providing system-level insights on how the central nervous system combines different sensory inputs into perceptual experiences and on how neural networks might handle the inherent uncertainty of our interactions with the surrounding environment. Bayesian perceptual inference could provide a framework to model central, system-level integration underlying human skin wetness sensing.

According to Bayesian perceptual models, sensory systems acquire knowledge on the properties of the surrounding environment to generate sensory priors (i.e., memories and neural representations) that help the processing of new sensory stimuli. Priors allow multimodal, noisy, and ambiguous sensory stimuli to be filtered efficiently, characterized, and used appropriately, according to the context (Körding and Wolpert 2004). This strategy helps optimize our ability to integrate current experiences efficiently and to act accordingly; thus such strategies are beneficial in rehabilitation after injury (Wolpert and Ghahramani 2000) and could be used in adaptation to using a prosthetic (Bensmaia and Miller 2014).

It is reasonable to hypothesize that the central decoding of skin wetness depends on multimodal integration, based on sensory priors. The repeated exposure to sensory cues arising from the contact with moisture could generate neural representations of how a wet stimulus feels, from an early age. Support for the role of prior-dependent multisensory integration in sensing wetness arises through the observation that illusions of wetness can be evoked in the absence of physical contact with moisture. This occurs when the individuals are in contact with stimuli (e.g., contact with a dry-cold object) that induce sen-

sations (e.g., coldness) resembling the ones associated with the "prior" for physical skin wetness (e.g., coldness given by evaporation of moisture) (Filingeri et al. 2013, 2014b, 2014c).

In an attempt to describe both the peripheral and central processes involved in skin wetness sensing, we recently developed a system-level empirical model (Fig. 2), centered on the hypothesis that the central perception of skin wetness is based on sensory priors (Filingeri et al. 2014a). This model proposes that skin wetness sensing occurs only in the presence of particular combinations of sensory cues. For example, under contact with external static moisture, skin wetness is experienced only if moisture is colder than the skin or if it evaporates from its surface. Similarly, if moisture is at temperatures above the skin's, or if evaporation is limited, wetness will not be sensed unless movement of moisture occurs over the skin and dynamic mechanical inputs are triggered. The optimal condition for wetness sensing is therefore the one where cold moisture moves across the skin. Under this condition, both cold and tactile afferents are stimulated. A lack of activation in these peripheral pathways can limit wetness perception, even when the skin is in physical contact with moisture. The recent observation that blindfolded individuals were not able to sense skin wetness during the static contact with warm moisture supports the view that, irrespective of the presence of physical moisture, a lack of stimulation of either cold or mechanical skin afferents hampers wetness sensing (Filingeri et al. 2015b).

Sensorimotor Implications of Skin Wetness Perception for Precision Grip

Sensation and perception play an important part in enriching our experience of the surrounding world, yet their ultimate purpose is to provide motivation to drive behaviors and actions aimed at protecting body homeostasis and ensuring survival. Evolutionarily, the perception of wetness in humans could have developed as way to help regulate thermal homeostasis (Filingeri and Havenith 2015). Extensive evidence supports the view that sensing skin wetness in humans is critical for behavioral thermoregulation, because perceiving changes in both ambient humidity and skin wetness has been shown to impact thermal comfort (Fukazawa and Havenith 2009), and thus thermoregulatory behavior (Schlader et al. 2010), in both healthy and clinical populations (e.g., individuals suffering from rheumatic pain; Strusberg et al. 2002). This "thermal homeostasis hypothesis" for wetness perception also applies to a number of other species (e.g., fruit flies, nematodes, cockroaches; Kim and Wang 2016), where wetness and humidity sensing is a highly conserved sensory mechanism, essential to ensure optimal function and survival in the living environment (Filingeri 2015). Aside from its importance in driving thermal behavior (Fukazawa and Havenith 2009; Gagge et al. 1967), there is evidence to suggest that sensing skin wetness could also contribute to precision grip and accurate object manipulation in humans (Adams et al. 2012; André et al. 2010; André et al. 2011).

Humans have evolved tremendous manual dexterity of the hands, which is dependent on complex sensorimotor integrations. The ability to grasp and hold objects between the thumb and the index finger, and to avoid slips, so-called precision grip, is one of the essential attributes of manual dexterity and an outstanding example of flexible sensorimotor integration

(Johansson and Flanagan 2009; Witney et al. 2004). In this respect, the presence of physical wetness on the skin or on the objects manipulated can alter the frictional dynamics of hand-object interactions (Westling and Johansson 1984).

Despite evidence indicating that tactile feedback is of fundamental importance to maintaining grip, avoiding slip, and ensuring optimal hand function (Bilaloglu et al. 2016; Johansson and Westling 1984; Saels et al. 1999), the implications of skin wetness perception for precision grip have received no attention to date. Researching the role of sensing skin wetness in sensorimotor integration could be relevant not only to better understand precision grip under normal hand function but also to develop human-like neuroprostheses that can provide realistic sensory feedback (Ackerley and Kavounoudias 2015; Chortos et al. 2016; Tabot et al. 2013). Here, we focus on how the presence of moisture or sweat on the skin influences object manipulation and on how skin wetness perception and thermotactile sensory feedback could be involved in motor adjustments preceding and contributing to the fine control of precision grip.

Overview of precision grip. The importance of precision grip in our everyday life becomes evident when this manual skill is impaired, for example, the struggle faced when trying to tie your shoelaces on a cold day. The cold-induced transient numbness of the fingers, and the related worsening of fine manipulation, provides a good example of how much we rely on precision grip for fundamental daily activities. This functional property of the human hand allows for a remarkable movement precision when handling, lifting, and manipulating objects. Holding a pen and writing, lifting a bottle of water, using a fork, or unlocking a door are all examples of common daily life activities that involve the use of a precision grip.

Since the seminal work of Johansson and Westling (Johansson and Westling 1984, 1987; Westling and Johansson 1984), we have made great progress in our understanding of the sensory and motor components, and of the central sensorimotor models involved in controlling precision grip (Johansson and Flanagan 2009; Prodoehl et al. 2009; Witney et al. 2004; Wolpert and Ghahramani 2000). When pinching and lifting an object (i.e., the simplest form of precision grip), we balance the grip force required to lift the object according to the load force deriving from the object itself (i.e., its weight) to avoid slip (Westling and Johansson 1984). One of the most important functional goals of precision grip is to avoid the object slipping from our fingers, which is especially pertinent when the object is wet.

The importance of this concept was demonstrated elegantly in showing that the amount of force used to lift an object gripped between the index finger and thumb is precisely scaled at a level that is always slightly higher than the load force of the object, at the minimum force required to prevent a slip (Johansson and Westling 1984). The difference between grip and load forces represents the so-called safety margin and ensures that a safe grip is maintained, and that accidental slip is prevented, when unexpected perturbations in the hand-object interaction occur (Augurelle et al. 2003). Under both static (e.g., lifting and holding) and dynamic (e.g., carrying) object manipulations, grip force is not fixed but changes with acceleration-dependent changes in load force (Saels et al. 1999). In this respect, slip ratio, i.e., the ratio between the minimum amount of force preventing slip and the corresponding load force (Johansson and Westling 1987), is important and is a measure of the coefficient of skin-object friction, a parameter that directly influences the force adjustments required to avoid slip during object manipulation (Adams et al. 2012).

Skin-object frictional properties can alter the dynamics of gripping during the preloading (i.e., when the object is first approached) and loading (i.e., when the object begins to be lifted) phases of grip, with the rate of change in grip force during those phases being greater when lifting a more than a less slippery surface (e.g., silk vs. sandpaper) (Johansson and Westling 1984). The modulation of grip force when manipulating slippery or rough objects seems dependent primarily on frictional, rather than textural, properties. Analyses of the mechanics of how we grip objects indicate that the complex adjustments in static and dynamic griping forces occur almost unconsciously and instantaneously (Witney et al. 2004). Corrective actions leading to changes in grip-to-load force ratios can commence as early as ~100 ms after contact with an object (Johansson and Flanagan 2009). This optimal grip control results from a complex interplay between sensory information arising from the skin's interaction with the object gripped (Vallbo and Johansson 1984) and motor inputs involved in the gripping action (Bui et al. 2013).

From a sensory perspective, Johansson and Westling (1987) reported the importance of afferent inputs from skin mechanoreceptors by showing that cutaneous anesthesia results in a significant degradation of gripping performance. This indicates that the skin mechanoreceptive apparatus is sufficient for coding the mechanical deformations occurring during skin-object interactions. Analysis of the coupling between mechanical events occurring during a grip-and-lift task, and the corresponding neural responses in skin mechanoreceptors, has demonstrated that initial contact between the skin and an object is signaled by FA1 and SA1 afferents, which code contact timing, direction of contact, friction, and local object properties. FA2 afferents code information related to transient mechanical events such as making and breaking contact (Augurelle et al. 2003; Johansson and Flanagan 2009; Johansson and Westling 1987; Witney et al. 2004). Cutaneous mechanosensory feedback seems to also be important for intrinsic excitatory drive to hand muscles during gripping. Cutaneous anesthesia has been shown to reduce maximal voluntary contraction force of muscles involved in gripping by >25% (Augurelle et al. 2003).

When digital anesthesia removes cutaneous mechanosensory feedback, lifting and scaling with load force is abnormal, yet still present (Augurelle et al. 2003). This observation indicates that the control of grip might rely not only on the direct firing of mechanosensitive afferents but also on additional sensory afference (e.g., mechanoreceptive input proximal to fingertip grasp; Häger-Ross and Johansson 1996). Muscle proprioceptive inputs have been shown to play an important role in providing information on object weight and limb position (Proske and Gandevia 2012; Witney et al. 2004; Yoshioka et al. 2011). Evidence also indicates that thermal afferent feedback alters the perception of force and of surface properties during object manipulation (Galie and Jones 2010; Green et al. 1979; Ho and Jones 2006; Stevens 1982; Stevens and Hooper 1982). It seems that a complex interplay between different sensory inputs (i.e., cutaneous mechanical and thermal, along with muscle proprioceptive) influences the fine

control of precision grip. This is supported by the observation that skin-object frictional conditions during skin-object interactions alter not only grip dynamics but also the conscious perception of surface tactile properties (Adams et al. 2012).

The impact of moisture and sweat on skin friction and the role of skin wetness perception in precision grip. The presence of moisture or sweat at the skin-object interface alters the dynamics of precision grip. Evidence indicates that variations in frictional parameters due to *1*) the presence of external moisture at the skin-object interface (Saels et al. 1999), *2*) skin hydration (André et al. 2011; Smith et al. 1997), and *3*) sweating levels (André et al. 2010) all alter the dynamics of precision grip (André et al. 2010; Saels et al. 1999). Westling and Johansson (1984) reported that individuals show an increase in grip force during a lifting task after they wash and dry their hands to remove any potential moisture/sweat on their skin. Similarly, by pharmacologically manipulating individuals' ability to sweat via administration of scopolamine (a muscarinic blockade that reduces palmar sweating), Smith et al. (1997) observed that individuals performing a grip and lifting task used lesser grip forces during reduced sweating. In this case, a decrease in skin moisture translates to lower skin-object friction (Adams et al. 2012). A simple experience can elucidate this physical concept: draw your finger over your desk, then wet it, and draw again. The desk will now feel rougher than the dry condition, because the moisture increases the drag on the skin rather than acting as a lubricant (Verrillo et al. 1999). Because grip force appears to be higher when slippery objects with lower skin-object friction are being held, a decrease in skin moisture and consequently in skin-object friction would therefore increase grip force requirements to maintain a safe grip. Skin moisture thus influences grip force but is not sufficient for grip control.

Although greater levels of moisture and higher skin-object friction translate to lower grip force requirements, this is not necessarily true for all levels of skin moisture. André et al. (2010) observed that during a dynamic precision grip task, individuals adjusted their finger pad moisture within a range producing skin-object frictional coefficients that were optimal for manipulation (i.e., requiring minimal grip force). Moisture levels above or below this optimal range produced a reduction in skin-object friction and an increase in grip force. In practical terms, it appears that too much moisture at the skin-object interface (e.g., when a very slippery object is being manipulated with wet hands), or too little (e.g., when a dry object is being manipulated with very dry hands), makes precision gripping a more effortful task. The implications for prosthetic innovation are that sensing skin wetness may not be necessary to improve grip control, but the addition of such a signal allows the more naturalistic and accurate manipulation of objects.

The observation that skin moisture and hydration levels both modulate grip dynamics implies that surface slipperiness and frictional properties must be first "sensed" during skin-object interactions, before being acted upon (Grierson and Carnahan 2006). Contact with slippery objects excites FA1 afferents more strongly than contact with a less slippery surface (Johansson and Flanagan 2009; Khamis et al. 2014b). Accordingly, it has been proposed that FA1 mechanoreceptors could be exquisitely sensitive to mechanical deformations induced by microslips occurring at the papillary surface of the fingers (Delhaye et al. 2012; Johansson and Flanagan 2009; Khamis et

al. 2014a). In this respect, the recent "slip hypothesis" proposes that cutaneous sensory coding of microslips could be indeed responsible for the force adjustments observed during lifting of slippery objects (Schwarz 2016). However, whether microslip coding contributes to the conscious experience of surface properties during object manipulation is currently unknown.

A great deal of knowledge is available on grip-slip interactions in roughness perception (Johnson and Hsiao 1992; Klatzky and Lederman 1999; Roland et al. 1998; Smith et al. 2002; Verrillo et al. 1999; Yoshioka et al. 2011). Gwosdow et al. (1986) showed that increases in sweating-induced skin wetness and in the friction between the skin and a fabric sliding over the forearm positively correlate with an increase in roughness perception of the fabric. Smith et al. (2002) have reported that when individuals slide their finger pad over a lubricated surface, the lubricant-dependent drop in skin-object friction results in a decrease in roughness perception. Skin-object friction also appears to influence the perception of dryness. Chen et al. (2009a) have shown that increases in friction during free manipulation of textile materials translate to a decrease in dryness perception. On the contrary, surfaces with low compliance, low friction coefficient, and high roughness are likely to be perceived as being dry (Chen et al. 2009b).

Less is known about the relationship between object surface properties and skin wetness. Bergmann Tiest et al. (2012b) demonstrated that an increase in mechanical cues in the form of stickiness can increase wetness discrimination during dynamic contact with a wet material. A reduction in mechanical cues via a reduction in skin-clothing intermittent contact during active sweating produces a significant reduction in whole body, as well as local skin, wetness perception (Filingeri et al. 2015a). Nonomura et al. (2012) provided insights on how individuals might discriminate between the skin's contact with water and thicker aqueous solutions when sliding their finger pad over a wetted glass surface. The authors reported that a frictional stimulus (average force: 0.46 N) with large acceleration could be one of the characteristic sensory cues associated with water discrimination. Interestingly, the skin-water frictional interaction recorded appeared to be so specific that an illusion of touching water could be induced in attending individuals by delivering vibrations at their finger pad that resembled the ones experienced during stick-slip interactions with water (Nonomura et al. 2012). The latter observation is conceptually in line with the illusion of skin wetness inducible via dry cooling (Filingeri et al. 2013, 2014b, 2014c).

Although the evidence above has highlighted how certain objects' surface properties (e.g., level of physical moisture and friction) alter the conscious perception of skin wetness, there is little evidence on the implications of these perceptual cues for grip control during object manipulation. In light of the multimodal (i.e., thermotactile) and synthetic nature of skin wetness perception (i.e., this perception can be induced or suppressed irrespectively of the actual presence of moisture on the skin) (Bentley 1900; Filingeri et al. 2013, 2015b), assessing its role in precision grip could offer the advantage of dissociating the relative importance of the sensory (i.e., thermotactile feedback, presence/absence of skin wetness perception) and physical components (i.e., surface properties, skin-object friction) involved in the central sensorimotor integration underlying optimal grip function. During a precision grip task, manipulating the thermal cues involved in the perception of skin wetness

could alter precision grip independently of moisture levels and skin-object frictional properties. Temperature has indeed been previously shown to sharpen tactile acuity (Stevens 1982), and cooling seems to increase heaviness perception (Stevens and Hooper 1982) and influence grasp efficiency (Nowak and Hermsdörfer 2003). If this were confirmed and grip dynamics could be altered purely on the basis of the level of skin wetness perception, this could indicate that the somatosensory cues involved in the central generation of skin wetness could be involved in the sensorimotor loop underlying optimal object manipulation.

Regarding sensorimotor integration, central processes offer a means for the predictive and efficient planning and execution of grip control (Wolpert and Ghahramani 2000). Anticipatory control strategies may influence how wet objects are grasped; thus other signals (e.g., visual) will prime behavior, such as the predetermined force to use. During grasp, ongoing salient sensory information will be used to monitor and update the grip force, in line with sensory priors. This includes incorporating tactile and thermal cues, and any perception of wetness generated from these may influence central motor strategies. It is important that prosthesis functioning takes into account these anticipatory and fast reactions, for predictive control during sensorimotor interactions. For example, it was recently demonstrated that, contrary to what had long been believed, the magnitude of the safety factor maintained during precision grip tasks is not invariant, but it is a flexible feature of gripping that changes depending on the dynamics of the environment within which manipulation occurs (i.e., the greater the unpredictability of the manipulation dynamics, the greater the safety factor adopted) (Hadjiosif and Smith 2015).

Deepening our understanding of these somatosensory mechanisms is clinically relevant, particularly as sensory dysfunction is being increasingly recognized to contribute to the motor deficits observed in well-known movement disorders (e.g., Parkinson's disease) (Patel et al. 2014). Importantly, being able to quantify the relative importance of specific sensory cues (e.g., thermotactile) in skin wetness perception and the role of this perception in optimizing and modulating predictive and reactive motor control while objects are precisely gripped, could prove extremely valuable to facilitate their replication within a sensory neuroprostheses (Bensmaia 2015; Davis et al. 2016; Saal and Bensmaia 2015). When neurological disorders (e.g., from Parkinson's disease to cerebellar disorders), as well as traumatic injuries and amputation, induce permanent impairments in sensory function and precision grip, the consequences on individuals' quality of life are often tremendous (Nowak and Hermsdörfer 2005). The opportunity to restore sensory signals (among which is skin wetness perception; see Kim et al. 2014) would mark a significant advance in the use and incorporation of prosthetic body parts for both amputees and sensory-impaired individuals in everyday life.

Implementing Complex Afferent Feedback in Neuroprosthetic Development

The implementation of cutaneous sensory feedback for missing body parts represents an immense step forward in the development and use of prostheses. The artificially generated afference closes the sensorimotor loop and could provide a large range of information, from ongoing signals about the prosthetic and its position in space that are important for self-awareness to delivering basic input about external contact through to complex touch experiences, such as sensing skin wetness. The generation of artificial cutaneous signals is not a simple task; as outlined above, there are numerous different types of thermoreceptive and mechanoreceptive channels (Fig. 1). To put this in perspective, there are ~17,000 myelinated mechanoreceptors in the glabrous skin of the human hand (Johansson and Vallbo 1979b), and unmyelinated C-fibers compose ~80% of the axons in peripheral nerves (including sympathetic innervations; Ochoa and Mair 1969; St John Smith et al. 2012). This represents a vast input, a lot of which is spontaneously active, and it is currently impossible to register and reproduce this level of afference. However, advances recently have been made in restoring some functional sensory feedback from prostheses with the use of electrical nerve stimulation.

The removal of a body part causes a deficit in peripheral afferent feedback. The loss of body part usage is evident; however, there are further detrimental effects, such as potential complications with a changed body image and with social relationships. This may include more minor body part losses, such as the loss of a tooth, which has a temporary effect, to major impacts, such as the loss of entire limbs. The implantation and connection of a sensory prosthesis is not trivial, and neither is the implementation of motor functionality. However, advances in these areas have made prosthetic body parts better integrated and tolerated for much longer periods of time; for example, the use of osseointegration (bone implants) provides increased stability and has a lower rejection rate (Hagberg and Brånemark 2009; Ortiz-Catalan et al. 2014; Palmquist et al. 2014).

Sensory neuroprostheses have been conceptualized since the 1970s, when an attempt was made to stimulate the median nerve during prosthetic use (Clippinger et al. 1974). In that case, it was possible to electrically stimulate the nerve to produce sensations of paresthesia that could be used to feedback pressure sensations during grasp. Further studies have used the same principle to elicit "nontactile" sensations that can be used to guide prosthetic use, such as in grasping actions (Dhillon et al. 2004; Horch et al. 2011; Raspopovic et al. 2014; Rossini et al. 2010). More recent work has attempted to reproduce tactile-like sensations for the complete integration and naturalistic use of a prosthetic, with some success (Davis et al. 2016; Oddo et al. 2016; Tan et al. 2014). These studies have found natural feeling sensations from the use of patterned stimulation intensity, such as tapping, pressure, moving touch, and vibration (Tan et al. 2014), and have found that roughness discrimination information can be transmitted (Oddo et al. 2016), by using multiple electrode contact points, around and in the nerve, respectively. These studies show that it is possible to produce relatively constrained areas of sensation through electrical stimulation of axons. Understanding the specific responses of afferents to skin stimulation, including wetness interactions, will aid in recovering these signals.

This neural stimulation approach relates to the technique of single-unit intraneural microstimulation, where it is possible to electrically stimulate individual nerve afferents in humans (Torebjörk et al. 1987). Although the technique relies on matching physiologically and electrically defined signals (and thus is not possible in missing body parts), it has provided

insights into "quantal" sensations generated from single afferents, which demonstrates that future neuroprostheses may be able to stimulate and generate touch sensations in individual channels. Furthermore, when a select few afferents are excited electrically, further sensations may be generated, such as the perception of a line (Sanchez Panchuelo et al. 2016), which extends to the possibility of multisensory percepts, such as wetness, in stimulating specific thermal and mechanoreceptive inputs.

One major issue in implementing sensory feedback in prostheses is the extent to which the end-organ, or structure of the receptor, further encodes facets of the tactile experience. Recent work has shown the importance of the receptor response properties for shaping tactile input (Lesniak et al. 2014; Pruszynski and Johansson 2014). The complexity and timing transmitted in these signals cannot easily be replicated through axonal nerve stimulation; rather, it is likely that the encoding of external interactions by the prosthetic itself will contribute more to developing this.

The transmission and interpretation of synthetic neural signals must occur at a high temporal resolution, at least in reproducing discriminative feedback. Here, millisecond pulse timing is essential to signal external interactions, such as in microslip (Westling and Johansson 1987) and microtexture (Weber et al. 2013), both of which are important in the perception of skin wetness. Understanding the fundamental, bottom-up peripheral signals contributes to recreating complex sensations. In wetness detection, a neuroprosthesis must faithfully encode both thermal and tactile interactions, where such external events may only represent a small change from "baseline" signals (e.g., detecting a fine mist of water). A theoretical issue also arising is in the selection of relevant over irrelevant (or even nuisance) signals, and whether these can be adapted, either automatically by the prosthesis or manually by the user. This may include the signaling of more extreme external stimuli, such as mechanical, thermal, or nociceptive inputs that produce painful sensations. These are beneficial to include, to avoid damage to the prosthesis, although it may be preferable to be able to switch these signals off in the event of prosthetic impairment or destruction.

Overall, the most pertinent neural signals to recover in preliminary sensory neuroprostheses will be the transmission of basic tactile feedback, i.e., signaling the timing (onset, duration and offset), and of touch and force feedback. Presently, the selective stimulation of thermoreceptive or nociceptive inputs has not been accomplished, and this will likely be more problematic due to the conduction of the majority of these messages via thin fibers, yet to signal wetness, a thermal component seems necessary (Ackerley et al. 2012b; Filingeri et al. 2013, 2014a). Future neuroprostheses should be designed to incorporate multifaceted aspects of cutaneous sensations, taking into account the additive effect from peripheral signals in creating centrally generated percepts, including aspects such as wetness, pleasure, and pain, and may even go beyond our own sensory boundaries.

Conclusions

The thermoreceptive and mechanoreceptive literature provides us with a breadth of knowledge into the complexities of these sensing mechanisms, and on the whole they are investigated separately. However, the few studies combining thermal and mechanical stimuli show that many types of mechanoreceptive afferent are sensitive to thermal changes, with individual signatures to heating and/or cooling. Because the encoding of the perception of skin wetness is likely signaled by both temperature and touch, it is important to consider all these sensory afferents when investigating its mechanisms and also when applying the knowledge, such as in sensory prostheses.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

D.F. conceived and designed research; D.F. and R.A. prepared figures; D.F. and R.A. drafted manuscript; D.F. and R.A. edited and revised manuscript; D.F. and R.A. approved final version of manuscript.

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