Why wet feels wet? A neurophysiological model of human cutaneous wetness sensitivity

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Filingeri D, Fournet D, Hodder S, Havenith G. Why wet feels wet? A neurophysiological model of human cutaneous wetness sensitivity. J Neurophysiol 112: 1457–1469, 2014. First published June 18, 2014; doi:10.1152/jn.00120.2014.—Although the ability to sense skin wetness and humidity is critical for behavioral and autonomic adaptations, humans are not provided with specific skin receptors for sensing wetness. It has been proposed that we “learn” to perceive the wetness experienced when the skin is in contact with a wet surface or when sweat is produced through a multisensory integration of thermal and tactile inputs generated by the interaction between skin and moisture. However, the individual roles of thermal and tactile cues and how these are integrated peripherally and centrally by our nervous system is still poorly understood. Here we tested the hypothesis that the central integration of coldness and mechanosensation, as subserved by peripheral A-nerve afferents, might be the primary neural process underpinning human wetness sensitivity. During a quantitative sensory test, we found that individuals perceived warm-wet and neutral-wet stimuli as significantly less wet than cold-wet stimuli, although these were characterized by the same moisture content. Also, when cutaneous cold and tactile sensitivity was diminished by a selective reduction in the activity of A-nerve afferents, wetness perception was significantly reduced. Based on a concept of perceptual learning and Bayesian perceptual inference, we developed the first neurophysiological model of cutaneous wetness sensitivity centered on the multisensory integration of cold-sensitive and mechanosensitive skin afferents. Our results provide evidence for the existence of a specific information processing model that underpins the neural representation of a typical wet stimulus. These findings contribute to explaining how humans sense warm, neutral, and cold skin wetness.

THE ABILITY TO SENSE HUMIDITY and wetness is an important attribute in the animal kingdom. For many insects, discriminating between dryness and wetness is vital for procreation and survival (Liu et al. 2007). Sensing wetness is also critical for humans, for both behavioral and autonomic adaptations. Perceiving changes in 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). From an autonomic perspective, decreases in ocular wetness seem to initiate the lacrimation reflex in order to maintain a tear film to protect the ocular surface (Hirata and Oshinsky 2012). Also, tactile roughness and wetness discrimination is critical for precision grip (Augurelle et al. 2003) and object manipulation (André et al. 2010). However, although the ability to sense wetness plays an important role in many physiological and behavioral functions, the neurophysiological mechanisms underlying this complex sensory experience are still poorly understood (Montell 2008).

In contrast with insects, in which humidity receptors subserving hygrosensation have been identified and widely described (Tichy and Kallina 2010), humans’ largest sensory organ, i.e., the skin, seems not to be provided with specific receptors for the sensation of wetness (Clark and Edholm 1985). Thus, as human beings, we seem to “learn” to perceive the wetness experienced when the skin is in contact with a wet surface or when sweat is produced (Bergmann Tiest et al. 2012) through a complex multisensory integration (Driver and Spence 2000) of thermal (i.e., heat transfer) and tactile (i.e., mechanical pressure and friction) inputs generated by the interaction between skin, moisture, and (if donned) clothing (Fukazawa and Havenith 2009). The hypothesis of wetness as a “perceptual illusion” shaped by sensory experience has been supported by our previous findings. We have recently shown that exposing the skin to cold-dry stimuli (resulting in cooling rates similar to those occurring during the evaporation of water from the skin) can evoke an illusion of local skin wetness (Filingeri et al. 2013, 2014a, 2014b). This could be due to the fact that we seem to interpret the coldness experienced during the evaporation of moisture from the skin as a signal of the presence of moisture (and thus wetness) on the skin surface. In line with this hypothesis, we have also observed that during static contact with a warm-wet surface (with a temperature warmer than the skin) no local skin wetness was perceived, as no skin cooling, and thus no cold sensations, occurred (Filingeri et al. 2014c).

These preliminary findings appeared to be in line with the Bayesian concept of perceptual inference (Knill and Richards 1996). According to this framework, sensory systems (such as the somatosensory system) incorporate implicit knowledge of the environment and use this knowledge (i.e., sensory experiences) to infer about the properties of specific stimuli (Geisler and Kersten 2002). As the sensory feedback received from the surrounding environment is by nature multimodal (i.e., involving different sensory cues), as well as noisy and ambiguous, perceptual systems are thought to perform online tasks aiming to predict the underlying causes for a sensory observation in a fashion that is considered as near optimal (Lochmann and Deneve 2011). In this context, humans have been shown to integrate the different sensory cues associated with an external stimulus and to infer the most probable multimodal estimate (i.e., perception) by taking into account the reliability of each...
sensory modality involved in the perceptual process (Ernst and Banks 2002; Weiss et al. 2002).

The potential ability of our neural systems to solve the inherent uncertainty associated with sensory interpretation in a probabilistic and predictive manner (Lochmann and Denève 2011) explains why many apparently idiosyncratic perceptual illusions (see, e.g., the effects of luminance contrast on the perception of motion velocity; Weiss et al. 2002) are instead what one would expect from a rational perceptual system (Geisler and Kersten 2002). Thus sensory illusions, such as the perception of wetness, can be used as a powerful method to gain conceptual and functional understanding of the sensory processing operated by specific sensory systems such as the somatosensory system (Lochmann et al. 2012).

In this respect, our previous work has shown that the cold sensations resulting from the afferent activity of the cutaneous cold-sensitive, myelinated Aδ-nerve fibers (with conduction velocities ranging from 5 to 30 m/s) (Campero et al. 2001) play a critical role in the ability to perceive skin wetness (Filingeri et al. 2013, 2014a, 2014b, 2014c). Furthermore, we have recently demonstrated that tactile inputs, which are likely to be encoded by cutaneous mechanosensory Aβ-nerve fibers (with conduction velocities ranging from 16 to 100 m/s) (Tsunozaki and Bautista 2009), could have a role in modulating the perception of skin wetness (Filingeri et al. 2014a). Thus these observations have led us to hypothesize that the central integration of coldness and mechanosensation, as subserved by peripheral myelinated A-nerve fibers, might be the primary neural process underpinning humans’ ability to sense wetness. However, what remains unclear is the individual roles of thermal and tactile cues and how these are integrated peripherally as well as centrally. If the multimodal integration of coldness and mechanosensation was the main neural process for sensing wetness, it would be reasonable to hypothesize that during the contact with a wet surface the absence of any coldness and mechanosensation, if either naturally (i.e., contact with a warm-wet or neutral-wet surface) or artificially (i.e., during a selective reduction in the activity of A-nerve fibers) induced, would result in a reduced cutaneous sensitivity to wetness. Hence, in the present study we used psychophysical methods to investigate the role of thermal and tactile afferents and their central integration in the perception of skin wetness under normal fiber function and under a selective reduction in the activity of A-nerve afferents.

We tested the hypothesis that under normal nerve fiber function wetness perception is primarily driven by the integration of cold and tactile inputs as subserved by A-nerve fibers. Furthermore, we hypothesized that during a selective reduction in the activity of A-nerve fibers the artificially induced reduction in cutaneous cold sensitivity and mechanosensitivity would translate in a significant reduction in the extent of perceived wetness. Finally, given the anatomical and functional differences in cutaneous thermal sensitivity and mechanosensitivity between hairy and glabrous skin (Abraira and Ginty 2013; Haggard et al. 2013; Pleger and Villringer 2013), here we investigated whether the proposed neurophysiological model of wetness sensitivity applies similarly to the forearm (i.e., hairy) as well as to the index finger pad (i.e., glabrous). As hairy and glabrous skin sites have been shown to differ in terms of innervation and particularly in terms of density of thermosensory and mechanosensory afferents as well as in their biophysical properties (e.g., thickness and thermal conductance) (Abraira and Ginty 2013), it was hypothesized that, because of the primary role of thermal cues in sensing wetness (Filingeri et al. 2013, 2014a, 2014b, 2014c), the higher thermal sensitivity of the hairy skin (due to its larger density of thermoreceptors and to its lower thermal conductance) (Norrell et al. 1999) would translate in wetness being perceived in larger magnitude on this skin site as opposed to the glabrous skin, despite the fact that latter presents a larger density of slowly adapting type I mechanosensory afferents, also known as Merkel cells (low-threshold mechanoreceptors transmitting acute spatial images of tactile stimuli with remarkably high spatial resolution) (Abraira and Ginty 2013), which could potentially contribute to an increase in the haptic perception of wetness on this type of skin.

**METHODS**

**Participants**

Thirteen healthy male university students (mean age 21 yr, SD 2; mean height 185 cm, SD 9; mean body mass 86 kg, SD 12) with no history of sensory-related disorders volunteered to participate in this study. All participants gave their informed consent for participation. The test procedure and the conditions were explained to each participant. The study design was approved by the Loughborough University Ethics Committee, and testing procedures were in accordance with the tenets of the Declaration of Helsinki.

A sample size calculation was performed in order to determine the minimum number of participants required to be able to detect a significant change in thermal sensitivity and mechanosensitivity as a result of the selective block protocol. Pilot tests data indicated that the difference in the thermal sensations of matched pairs (block vs. no-block trials) was normally distributed with a standard deviation of ~10 arbitrary units (a.u.). As we set the true difference in the mean thermal sensation of matched pairs at a value of 15 a.u., it was calculated that a minimum number of 12 participants was needed to be able to reject the null hypothesis that this response difference is zero with probability (power) 0.8. The type I error probability associated with this test of this null hypothesis (α) was 0.05. Sample size calculations were performed with Power and Sample Size Calculation version 3.0 2009 (Vanderbilt University).

**Experimental Design**

Participants took part in three experimental trials, during which the same quantitative sensory test was administered. The hairy skin of the ventral side of the left forearm (i.e., middistance between elbow and wrist) and the glabrous skin of the left index finger pad were exposed to contact with a warm-wet (35°C), a neutral-wet (30°C), and a cold-wet (25°C) stimulus during three phases: static, dynamic, and evaporation (i.e., after contact). During contact with the stimuli, participants reported their local thermal and wetness perceptions on a hand-scored 100-mm visual analog scale for thermal (anchor points: hot and cold) and wetness (anchor points: completely dry and completely wet) perception, while skin temperature at the contact site was continuously monitored. The three experimental trials differed with regard to the presence or absence of a selective reduction in the activity of A-nerve fibers and to the skin site stimulated. All 13 participants performed one trial during which no nerve block was performed (NO-BLOCK) and the skin of the forearm and finger pad were exposed to the wet stimuli and two separate trials during which a selective reduction in the activity of A-nerve fibers was performed through local compression ischemia and the skin of the forearm (FA-BLOCK) or finger pad (FI-BLOCK) was exposed to contact with
the wet stimuli. Trials were performed in a balanced order, on separate days, with at least 72 h in between.

The thermal stimuli were delivered by a thermal probe (Physitemp Instruments) with a contact surface of 25 cm² and a weight of 269 g. To make the contact with the probe’s surface wet, test fabrics (100% cotton) with a surface of 100 cm² were placed on the thermal probe and fixed by an elastic band. These were wetted with 2,000 µl of water at ambient temperature (~23°C) with a variable-volume pipette (SciQuip, Newtown, UK). To ensure that the wet fabric would reach the required temperature (i.e., 35°C, 30°C, or 25°C), the contact temperature between the probe and the test fabric was monitored with a thin thermocouple (0.08-mm wire diameter, 40 gauge; 5SRTC-TT-TI-40-2M, Omega, Manchester, UK) placed on the thermal probe surface. Also, local skin temperature (Tsk) at the contact site of stimulation was measured continuously through the application of a thermocouple on the ventral side of the forearm or index finger pad with Transpore tape (3M, Loughborough, UK), with the sensor tip touching the skin but not covered by tape. Probe-fabric temperature as well as Tsk were monitored with a Grant Squirrel SQ2010 data logger (Grant Instruments, Cambridge, UK).

During all the trials, participants rested in a seated position in a thermoneutral environment (air temperature: ~23°C; relative humidity: ~50%). Participants were informed only about the skin site subjected to the stimulation and the trial to be performed (block vs. no block). No information was made available on the type and magnitude of the stimulation, to limit any expectation effects. To make this possible, an S-shaped wooden panel (width: 81 cm; height: 74 cm; height: 60 cm) was placed on a table. A hole (width: 12 cm; height: 13 cm) in the panel allowed participants to insert their left forearm through the panel. This experimental setup did not allow the participants to see the stimulated area.

Experimental Protocols

NO-BLOCK trial. In the NO-BLOCK trial, no compression ischemia was performed and participants interacted actively with the warm-wet, neutral-wet, and cold-wet stimuli. Forearm and index finger pad skin sites were tested separately within this trial, allowing a 5-min interval between them.

The thermal probe was secured with surgical tape on the side of the table that was not visible to the participants, with the thermally controlled surface facing upward. Prior to interacting with each wet stimulus, and in order to set a baseline Tsk of 30°C, participants were instructed to insert their left arm through the hole in the panel and place the forearm or index finger pad for 30 s on the dry thermal probe, which was set at 30°C. Participants then removed the arm from the thermal probe, placed it on the side of the table visible to them, and waited 1 min for the first stimulus to be prepared. During this time, the probe was set to the required temperature (i.e., 35°C, 30°C, or 25°C) and the test fabric was secured to the probe and then wetted with the pipettor. Pilot tests indicated 1 min as the time required for the wet test fabric to reach the selected temperature. Once the stimulus preparation was completed, the interaction with the wet stimulus was initiated.

This consisted of three phases (each lasting 10 s): static, dynamic, and evaporation (i.e., after contact). First, participants were instructed to insert their left arm through the hole in the panel and to lower it until the forearm or index finger pad was in full contact with the thermal probe. As soon as they were in static contact, they were encouraged to rate their local thermal and wetness perceptions by marking a point on the thermal and wetness scales they were provided with on the side of the table that was visible to them (response time ~5 s). Then participants were asked to move the forearm or index finger pad forward (~2.5 cm) and backward (~2.5 cm) twice while maintaining full contact with the thermal probe. At the end of this dynamic interaction they were asked again to rate their local thermal and wetness perceptions (response time ~5 s). Finally, they were asked to lift the forearm or index finger pad up from the thermal probe, thus allowing evaporation of any residual moisture on the skin, and as soon as they were not in contact with the probe, to rate their local thermal and wetness perceptions for the last time (response time ~5 s). This sequence (i.e., setting the baseline skin temperature, preparing, and Yarnitsky and Ochoa 1990), our pilot studies indicated that the compression ischemia impacts transmission in myelinated A fibers before C fibers (i.e., primarily subserving conscious warmth and pain sensitivity) are affected (Torebjörk and Hallin 1973). Compression ischemia was induced by inflating a sphygmomanometer cuff on the upper arm to a suprasystolic pressure (i.e., 140 mmHg) for a maximum duration of 25 min. During the compression ischemia protocol, thermal sensitivity to warm (i.e., 35°C) and cold (i.e., 25°C) stimuli as well as mechanical sensitivity to light brush were checked every 5 min. It deserves mention that, despite changes in mechanosensitivity and cold sensitivity, the maximal duration of the compression ischemia was set to 25 min in order to limit the discomfort and pain the participants could experience underneath the cuff (Note: this duration does not include the subsequent stimulation with the wet stimuli, whose approximate duration was ~8 min). Although the literature reports compression blocks lasting between 27 and 60 min and performed with pressures up to 100 mmHg above systolic pressure (see, e.g., Davis 1998; Yarnitsky and Ochoa 1990), our pilot studies indicated that the duration chosen as well as the pressure used were sufficient to induce a gradual reduction in cold sensitivity and mechanosensitivity, while keeping participants’ overall discomfort at a minimum. Indeed, during our preliminary testing, participants could not bear the 140-mmHg cuff pressure for longer than 35–40 min because of the excessive discomfort experienced underneath the cuff.

Prior to the application of the compression ischemia protocol, instrumentation and baseline measurements were performed. Particip-
pants were asked to sit on a chair for 15 min, at the end of which resting blood pressure was measured from the left wrist with a digital wrist blood pressure monitor (Speidel and Keller, Jungingen, Germany) while the arm was supported at heart level. Participants then inserted their left arm through the hole in the panel and laid it down with the palm facing upward while a 13-cm-wide sphygmmomanometer cuff (Hokanson, Bellevue, WA) was placed around the arm (i.e., middistance between shoulder and elbow). The sphygmmomanometer cuff was connected to a custom-made cuff inflator. According to the experimental trial, a thermocouple was then taped to the ventral side of the forearm or to the index finger pad to record Tsk throughout the test. An 8-mm optic probe was taped to the ventral side of the forearm (proximal to the elbow joint) and connected to a laser Doppler monitor (Moor Instruments, Axminster, UK) to record skin blood flow. Finally, to allow thermal stimulation of the skin, the thermal probe, set at 30°C, was secured with tape on the forearm or index finger pad (with the thermally controlled surface in full contact with the skin), where it rested during the first part of the test.

After instrumentation, baseline Tsk and skin blood flow were recorded for 5 min while participants were asked to maintain a comfortable seated position, having their left arm lying on the left-hand side of the table (which was not visible to them) and their right arm on the right-hand side, where the rating scale and washable marker were positioned to allow ratings of sensation when required. This position was maintained throughout the whole test. At this point before compression ischemia cutaneous thermal sensitivity and mechanosensitivity were tested as follows: the thermal probe’s temperature was first set to 35°C (i.e., warm-dry stimulus), and as soon as this temperature was reached (response time <4 s) participants were immediately asked to rate their thermal sensation only, by marking a point on the thermal sensation scale. The thermal probe was then reset to 30°C. As soon as the Tsk returned to 30°C (this was monitored online on the data logger recording from the thermocouple placed on the skin site stimulated) the thermal probe’s temperature was changed to 25°C (i.e., cold-dry stimulus), and as soon as this temperature was reached participants were asked again to rate their thermal sensation only. The thermal probe was then reset to 30°C. As soon as the skin near the stimulated site was gently touched with a cotton pad and participants were asked to report verbally whether they could sense the touch. As soon as the baseline measurements were completed, the custom-made cuff inflator was started, the sphygmmomanometer cuff was inflated with the required pressure (time to reach the pressure: ~5 s), and the compression ischemia protocol was initiated. The cutaneous sensitivity test was then repeated as above every 5 min. When the inability to perceive the light brush was observed, along with a reduction in thermal sensitivity to the cold stimulus, the thermal probe was removed from the skin site, and the warm-wet, neutral-wet, and cold-wet stimuli were prepared and then applied according to a protocol identical to that performed during the NO-BLOCK trial (i.e., static, dynamic, and evaporation phases), with the only difference being that the investigator applied the thermal probe instead of the participants placing their forearm or finger pad on it.

Statistical Analysis

In the present study, the independent variables were the temperature of the stimuli (i.e., 35°C, 30°C, and 25°C), the different phases of stimulation (i.e., static, dynamic, and evaporation), the skin site stimulated (i.e., forearm and index finger pad), and the condition (i.e., presence or absence of a selective reduction in A-fiber activity). The dependent variables were local Tsk, thermal sensation, and wetness perception. All data were first tested for normality of distribution and homogeneity of variance with Shapiro-Wilk and Levene’s tests, respectively. To investigate the role of thermal and mechanical cues on cutaneous thermal and wetness sensitivity, and whether differences exist between hairy and glabrous skin, data from the NO-BLOCK trial were analyzed by a three-way repeated-measures ANOVA, with temperature of the stimuli (3 levels), phase of stimulation (3 levels), and skin site (2 levels) as repeated-measures variables. To investigate whether the compression ischemia protocol was effective in selectively reducing A-nerve fiber function in both forearm and index finger pad skin sites, thermal ratings recorded prior to and at the end of the protocol (i.e., just before the wet stimuli were applied) were compared for both warm and cold stimulations by using paired t-tests. To investigate whether a reduction in cutaneous cold sensitivity and mechanosensitivity decreased the ability to perceive skin wetness, data from the NO-BLOCK and BLOCK trials were analyzed separately for the forearm and index finger pad by a three-way repeated-measures ANOVA, with condition (2 levels), temperature of the stimuli (3 levels), and phase of stimulation (3 levels) as repeated-measures variables. Data were tested for sphericity, and if the assumption of sphericity was violated Huynh-Feldt or Greenhouse-Geisser corrections were undertaken to adjust the degrees of freedom for the averaged tests of significance. Estimated marginal means and 95% confidence intervals (CIs) were used to investigate the main effects and interactions of the variables. When a significant main effect was found, Tukey’s post hoc analyses were performed. To quantify the power associated with the statistically nonsignificant results, observed power was computed with \( \alpha = 0.05 \) and reported. In all analyses, \( P < 0.05 \) was used to establish significant differences. Furthermore, according to Curran-Everett and Benos (2004), precise \( P \) values were interpreted as follows: \( P > 0.1 \) are consistent with a true zero effect; \( 0.05 < P < 0.1 \) data suggest that there may be a true effect that differs from zero; \( 0.01 < P < 0.05 \) data provide good evidence that the true effect differs from zero; and \( P < 0.01 \) provide strong evidence that the true effect differs from zero. Data were analyzed with SPSS Statistics 19 (IBM, Armonk, NY) and are reported as means and SD and 95% CI.

RESULTS

Cutaneous Sensitivity to Wetness Under Normal A-Nerve Fiber Function (NO-BLOCK Trial)

During the initial static contact with the warm-wet, neutral-wet, and cold-wet stimuli, forearm skin and index finger pad Tsk respectively increased, remained unchanged, or decreased (Fig. 1, A and C). These variations in Tsk remained stable during the following dynamic phase. During the evaporation phase Tsk started to return to prestimulation values after the warm-wet and cold-wet stimulations, whereas it started to decrease after the neutral-wet stimulation.

As a result, participants reported thermal sensations that varied significantly according to the temperature \( F = 28.8(1,2,12,9,9), \ P < 0.0001 \) and phase of interaction \( F = 6.3(2,2,2,2), \ P = 0.007 \) with the wet stimuli. A trend was observed, with the forearm being more thermally sensitive than the finger pad \( F = 3.6(1,11), \ P = 0.085 \), observed power = 0.4. Overall, thermal sensations matched the variations observed in local Tsk: with the warm-wet stimulus resulting in warmer sensations, the neutral-wet stimulus in neutral sensations, and the cold-wet stimulus in colder sensations (Fig. 1, E and G).

With regard to wetness sensitivity, although all the stimuli presented the same level of physical wetness (i.e., 20 \mu\text{L}/cm²), participants reported wetness perceptions that increased significantly with decreasing contact temperatures \( F = 5.3(2,2,4) \), \( P = 0.012 \) (Fig. 2A). Also, wetness perception increased significantly during the dynamic as opposed to the static contact \( F = 11.5(2,2,4) \), \( P < 0.0001 \) (Fig. 2B). Overall, a trend was observed in the interaction between temperature and phase of stimulation.
This indicated that during the static phase the cold-wet stimulus was perceived as “wetter” than the warm-wet and neutral-wet stimuli and that during the dynamic and evaporation phases, wetness perceptions increased for all stimuli (Fig. 1, I and K). Finally, a trend of the effect of skin site on wetness perception was observed \( F(3,12) = 3.5, P = 0.086 \), observed power = 0.4, with the forearm showing a tendency in having a higher sensitivity to wetness (mean = 30.4 a.u.; CI = 21.8, 39.9 a.u.) than the index finger pad (mean = 18.2 a.u.; CI = 8.3, 28.1 a.u.).

Overall these results indicate that the perception of skin wetness was driven by the coldness experienced, and that when no coldness was perceived (e.g., warm-wet and neutral-wet stimulations), participants’ ability to sense wetness relied on the mechanical inputs generated during the dynamic interaction with the wet surface.

Selective Reduction in Activity of A-Nerve Fibers

To test the effectiveness of the selective reduction in the activity of A-nerve fibers, during the compression ischemia protocol thermal sensitivity to warm (i.e., 35°C) and cold (i.e., 25°C) dry stimuli as well as mechanical sensitivity to light brush were checked every 5 min. As a result of the protocol, a statistically significant reduction in thermal sensitivity to cold was observed, both in the forearm (mean difference = −17.3 a.u.; CI = −29.0, −5.7 a.u.; \( t = −2.6; \) 2-tailed \( P = 0.022 \); Fig. 3A) and index finger pad (mean difference = −16.8 a.u.; CI = −25.9, −7.7 a.u.; \( t = −1.5; \) 2-tailed \( P = 0.002 \); Fig. 3B). No significant differences in thermal sensitivity to warmth were observed at the end of the selective block protocol, either in the forearm (mean difference = +5.1 a.u.; CI = −15.9, 15.9 a.u.; \( t = 1.04; \) 2-tailed \( P = 0.32 \); Fig. 3C) or in the index finger pad (mean difference = −5.9 a.u.; CI = −14.4, 2.6 a.u.; \( t = −1.5; \) 2-tailed \( P = 0.15 \); Fig. 3D). As the warm and cold dry stimuli produced the same relative variations in local \( T_{sk} \) throughout the compression ischemia protocol (Fig. 4), these results indicate that this procedure was effective in selectively reducing cutaneous cold sensitivity of both forearm and finger pad, while keeping warmth sensitivity intact. With regard to mechanosensitivity, at the end of the compression ischemia protocol 2 of 13 participants were not able to sense the light brush on the forearm (FA-BLOCK trial), whereas during the FI-BLOCK trial 12 of 13 participants were not able to sense the light brush on the finger pad.
Changes in cold sensitivity and mechanosensitivity occurred earlier for the finger pad than for the forearm. For 11 of 13 participants, the selective block lasted 20 min during the FI-BLOCK trial and 25 min during the FA-BLOCK trial. It deserves mention that the selective block resulted in paradoxical heat sensations during cold stimulation in four participants in the FA-BLOCK trial and six participants in the FI-BLOCK trial. Before the application of the selective block, average values for resting systolic and diastolic pressure were 135 mmHg (SD 8) and 66 mmHg (SD 6), respectively.

Cutaneous Sensitivity to Wetness Under Selective Reduction of A-Nerve Fiber Function

As soon as the compression ischemia protocol proved effective, the quantitative sensory test was initiated. The results of the sensory test are presented individually for the forearm and then for the finger pad. Similar outcomes were observed for both forearm and finger pad during contact with the wet stimuli, after cold sensitivity and mechanosensitivity were reduced with the selective block protocol.

With regard to the forearm, during the initial static contact with the warm-wet, neutral-wet, and cold-wet stimuli forearm $T_{sk}$ showed variations similar to those recorded during the NO-BLOCK trial (Fig. 1B). However, a significant effect of the compression protocol [$F = 10.6_{(1,11)}, P = 0.008$] was found on thermal sensation. During the contact with the warm-wet and neutral-wet stimuli, participants’ thermal sensations did not differ significantly between NO-BLOCK and FA-BLOCK trials. However, as a result of the same cold-wet stimulus applied to the forearm, significantly “less cold” thermal sensations were reported during the FA-BLOCK trial (CI 39.7, 65.5 a.u.) than during the NO-BLOCK trial (CI 61.3, 82.5 a.u.) ($F = 13.7_{(1,12)}, P = 0.003$) (Fig. 1F). These results confirmed that at the time of application of the wet stimuli the forearm presented a reduced thermal sensitivity to cold.

This artificially induced reduction in cold sensitivity translated into a reduced perception of wetness of the forearm (Fig. 1J). Overall, the magnitude of perceived wetness was significantly reduced during the FA-BLOCK trial (CI = 4.9, 18.8 a.u.) compared with the NO-BLOCK trial (CI = 21.8, 39 a.u.) [$F = 13.7_{(1,12)}, P = 0.003$] (Fig. 5A). A trend in the
interaction between the effect of the block and the temperature of the stimuli was observed \( F = 3.2(2,24), P = 0.07, \) observed power \( = 0.5 \), with the greatest reduction in perceived wetness occurring during the cold-wet stimulation (see comparison between Fig. 1, I and J). Finally, a significant interaction between condition and phase of stimulation was found \( F = 11.7(2,24), P < 0.0001 \). As opposed to the NO-BLOCK trial, during which wetness perception increased from static to dynamic and evaporation, during the FA-BLOCK trial no changes in the forearm wetness perception from static to dynamic and a decrease from dynamic to evaporation occurred (Fig. 2D). Overall these results indicate that the significant reduction in the magnitude of perceived wetness observed during the FA-BLOCK trial was mainly due to the reduced cutaneous cold sensitivity and mechanosensitivity of the forearm.

Similar results were observed during the index finger pad contact with the wet stimuli (i.e., FI-BLOCK trial). During the initial static contact with the warm-wet, neutral-wet, and cold-wet stimuli, finger pad Tsk respectively increased (i.e., warm-wet and neutral-wet) or decreased (i.e., cold-wet) (Fig. 1D). As a result of the contact with the warm-wet and cold-wet stimuli, “less warm” and “less cold” thermal sensations were reported during the FI-BLOCK trial than during the NO-BLOCK trial (Fig. 1H). This interaction between condition (i.e., block vs. no block) and temperature of the stimuli was found to be statistically significant \( F = 13.1(1.5,17.6), P = 0.001 \). These results indicated that at the time of application of the wet stimuli the index finger pad presented a reduced thermal sensitivity to warmth and cold. This translated into a reduced sensitivity to wetness (Fig. 1L). A significant effect of condition \( F = 13.9(1,12), P = 0.003, \) a trend in temperature of the stimuli \( F = 2.9(2,24), P = 0.072, \) observed power \( = 0.5 \), and a significant effect of phase of stimulation \( F = 5.9(2,24), P = 0.008 \) were found on wetness perception (Fig. 2E).

Overall wetness sensitivity was significantly reduced during the FI-BLOCK trial (CI = 0, 2.5 a.u.) compared with the NO-BLOCK trial (CI = 8.3, 28.1 a.u.) (Fig. 5B). A significant interaction between condition and phase of stimulation was found \( F = 5.7(2,24), P = 0.001 \). As opposed to the NO-BLOCK trial, during which wetness perceptions increased from static to dynamic, during the FI-BLOCK trial no changes were observed from static to dynamic to evaporation (Fig. 2F). Overall these results reflect those observed with the forearm during the FA-BLOCK trial and indicate that the significant reduction in wetness sensitivity observed on the finger pad during the FI-BLOCK trial was mainly due to the reduced cutaneous thermal sensitivity and mechanosensitivity of this skin site.

**Fig. 3.** Ratings for thermal sensation as a result of the cold (25°C) and warm (35°C) stimuli as recorded before (Pre-BLOCK) and at the end of (i.e., just before application of wet stimuli, Post-BLOCK) the compression ischemia protocol. A and C show average and individual ratings for thermal sensation for the forearm. B and D show average and individual ratings for thermal sensation for the finger pad. Mean difference (group average \( n = 13 \)) and 95% CI between Pre and Post-BLOCK are also shown. One main tendency is illustrated. At the end of the BLOCK trials, thermal sensitivity on the cold side was significantly reduced while no significant changes in sensitivity on the warm side occurred, both for forearm and finger pad. Data are reported as means (group average \( n = 13 \)) and 95% CI (vertical lines).
DISCUSSION

The present study focused on the role of cutaneous thermal and tactile afferents and their central integration in the ability to sense wetness. By exposing hairy and glabrous skin sites to static and dynamic contact with warm-wet, neutral-wet, and cold-wet stimuli characterized by the same moisture content (i.e., 20 μl/cm²), we demonstrated that during a static contact wetness perception increases with decreasing contact temperatures and that during a subsequent dynamic interaction wetness perception increases regardless of the thermal inputs available. Also, we demonstrated that when cutaneous cold sensitivity and mechanosensitivity were significantly diminished through a selective reduction in the activity of A-nerve afferents, the extent of perceived wetness was also significantly reduced, on both the forearm and index finger pad. Finally, a trend was observed, with the extent of perceived wetness being higher on the hairy than on the glabrous skin.

In summary, our results indicate that the central integration of conscious coldness and mechanosensation, as subserved by peripheral myelinated A-nerve fibers, could be the primary neural process underpinning humans’ ability to sense wetness. To our knowledge the present study is the first to provide evidence in support of the hypothesis that a specific information processing model for cutaneous wetness sensitivity exists and that this is based on A-type somatosensory afferents. Given these outcomes, we developed the first neurophysiological model of human cutaneous wetness sensitivity (Fig. 6).

A Neurophysiological Model of Cutaneous Wetness Sensitivity

The proposed neurophysiological model is based on the concept of Bayesian perceptual inference for which sensory processing is considered an inference problem (Knill and Richards 1996). Given noisy and ambiguous sensory inputs (such as thermal and mechanical stimuli on the skin), the brain is thought to estimate which events caused these inputs (e.g., the presence or absence of physical wetness on the skin), on the basis of prior knowledge that is acquired and shaped by...
sensory experience (Lochmann et al. 2012). In our proposed information processing model, two main neural pathways are suggested to subserve cutaneous wetness sensitivity: one referring to the afferent activity of cold-sensitive Aβ-nerve fibers (projecting through the spinothalamic tract) and one referring to the afferent activity of mechanosensitive Aδ-fibers (projecting through the dorsal-column medial lemniscal pathway). The outcomes of this study have indeed indicated that in order to sense cutaneous wetness a multimodal integration of thermal (i.e., cold) and mechanical sensory inputs had to take place (Fig. 6A). From a functional point of view, this was confirmed by the fact that when the activity of A-nerve fibers was selectively reduced the extent of perceived wetness was also significantly reduced (Fig. 6B). From a central processing point of view, this was confirmed by the fact that, although all the stimuli had the same moisture levels, warm-wet and neutral-wet stimuli were sensed as significantly less wet than the cold-wet stimulus.

Perceptual learning and somatosensory decision making could contribute to explaining why the central nervous system processes sensory information about the perception of wetness in such a fashion (Pleger and Villringer 2013). As the skin seems not to be provided with hygroreceptors (Clark and Edholm 1985), we hypothesized that the primary and second-
ary somatosensory cortices, the insular cortex (a cortical region involved in cold temperature sensation) (Craig et al. 2000), as well as the posterior parietal lobe (a cortical region concerned with integrating the different somatic sensory modalities necessary for perception) (McGlone and Reilly 2010) could be involved in generating a neural representation of a “typical wet stimulus.” This could be based on the multimodal transformation (i.e., information from one sensory modality can be transformed into a map or reference frame defined by another modality) of the somatosensory inputs generated when the skin is physically wet (Haggard et al. 2013). As the sensory inputs associated with the physical experience of wetness are often generated by heat transfer in the form of evaporative cooling (Ackerley et al. 2012) and mechanical pressure in the form of friction and stickiness (Adams 2013), the typical neural representation of a wet stimulus might rely on perceiving coldness and stickiness. As for perceptual learning and somatosensory decision making (Pleger and Vilkinger 2013), this neural representation could be transformed into a firing rate code, representing the wet stimulus, and then associated to the perception of wetness. Hence, only if the memorized combination of stimuli (i.e., coldness and stickiness) as coded by the specific afferents (i.e., A-nerve fibers) is presented will wetness be sensed. In the occurrence of physical wetness on the skin, the top-down processes (i.e., combination of thermal and mechanical sensory afferents) as well as the top-down processes (i.e., inference of the potential perception based on the neural representation of a typical wet stimulus) might therefore interact in giving rise (or not) to the perception of wetness (Lochmann and Deneve 2011).

At this point, however, although perceiving coldness and stickiness is likely to be determinant in the ability to process wetness at a central level, studies by Gerrett et al. (2013) and everyday experience suggest that we are able to sense wetness even in the absence of coldness (e.g., during exposure to warm, humid environments or when in contact with warm water). In these particular conditions, the mechanical and pressure-related sensations resulting from the afferent information generated by cutaneous mechanosensitive fibers could therefore play a critical role in the ability to sense wetness. On the basis of the results of this study, as well as the available literature, we hypothesized possible mechanisms through which wetness is sensed, according to the sensory inputs available when the skin is in contact with warm, neutral, or cold moisture.

Cutaneous Sensitivity to Warm, Neutral, and Cold Wetness

Figure 6, C and D, shows the process through which warm moisture could be sensed. When the skin is in static contact with warm moisture (i.e., temperature above $T_{sk}$), no activation of cold-sensitive $\alpha$-nerve fibers occurs, and only C-fibers (subserving conscious warmth sensitivity) and $\alpha$-$\beta$-nerve fibers (subserving light touch) are involved in the somatosensation of moisture (Fig. 6C). In this scenario, as $\alpha$-$\beta$-nerve fibers are the only nerve fibers available within the processing model, cutaneous wetness will be sensed only if a higher level of mechanosensory afferents, i.e., a dynamic interaction between skin and warm moisture, occurs (Fig. 6D). A similar mechanism applies if the skin is in contact with neutral moisture (i.e., with a temperature equal to $T_{sk}$) (Fig. 6, E and F). In support of this, Bergmann Tiest et al. (2012) have recently observed that during the interaction with wet materials (i.e., cotton wool and viscose), Weber fractions for wetness discrimination thresholds decreased significantly when individuals were allowed dynamic as opposed to static touching. This indicated that individuals’ cutaneous sensitivity to wetness was increased by a higher availability of mechanosensory afferents, as occurring during the dynamic exploration of the wet materials. The authors concluded that when thermal cues (e.g., thermal conductance of a wet material) provide insufficient sensory inputs individuals seem to use mechanical cues (e.g., stickiness resulting from the adhesion of a wet material to the skin) to aid them in the perception of wetness.

In line with Bergmann Tiest et al. (2012), in this study we observed that the lack of thermal inputs (i.e., in the case of neutral wetness) translated in a reduced sensitivity to wetness, until a dynamic interaction with the wet stimuli was allowed and a higher level of mechanosensory afferents was then made available for central integration (Fig. 6, E and F). However, and in addition to the findings of Bergmann Tiest et al. (2012), in our proposed neural model we suggest that the extent of perceived wetness is reduced, and mechanosensory afferents are therefore more important, not only when thermal cues are insufficient but also when these are the “incorrect” cues. This seems to happen when in contact with warm moisture (Fig. 6, C and D). Although in this case thermal cues in the form of warm sensations are available, as these are generated by sensory afferents (i.e., C-nerve fibers) that are “outside” the proposed model for wetness (i.e., relying on A-nerve fibers) and that are not associated with the neural representation of a “typical wet stimulus,” wetness sensitivity to warm moisture is reduced unless more mechanosensory afferents are activated (i.e., stickiness due to the skin friction with the wet stimulus) (Adams 2013; Gerhardt et al. 2008). In line with this, we have recently shown that during static contact with a wet surface warm stimuli (i.e., temperature above $T_{sk}$) can suppress the perception of cutaneous wetness (Filingeri et al. 2014c).

Behavioral and learning components could contribute to the concept of “incorrect” thermal cues. Psychophysical studies have indeed shown that as humans we tend to associate the blend of warmth and light pressure more with the perception of oiliness (Cobbey and Sullivan 1922) than with the perception of wetness (Bentley 1900). Everyday life further provides evidence in support of why, in the absence of stickiness, warm sensations only seem not to be associated with the perception of wetness. For example, a bleeding nose is an experience we usually become aware of only after this has been pointed out to us and the “wet area” has been haptically explored by touch. This could be due to the fact that blood temperature ($\sim 37°C$) is usually higher than $T_{sk}$ ($\sim 30°C$) (Mekjavic and Eiken 2006).

A combination of anatomical, physiological, and learning factors could also explain the trend observed with the forearm (i.e., hairy skin) being more sensitive to wetness than the finger pad (i.e., glabrous skin). Hairy and glabrous skin sites differ in terms of innervation and particularly in terms of density of thermo- and mechanosensory afferents as well as in their biophysical properties. As observed in this study and as previously shown (Norsell et al. 1999), hairy skin seems indeed to be more sensitive to thermal stimuli than glabrous skin, which on the contrary presents higher spatial acuity. From the receptor point of view, this could be due to the fact that although both glabrous and hairy skin sites are innervated with
slowly adapting type 1 mechanosensory afferents, also known as Merkel cells (low-threshold mechanoreceptors transmitting acute spatial images of tactile stimuli with remarkably high spatial resolution), glabrous skin presents a higher density of these specialized organs for tactile discrimination, a fact that could explain the higher spatial acuity to mechanical stimuli of this type of skin (Abaira and Ginty 2013). From a biophysical point of view, the presence of a thicker stratum corneum (i.e., the outermost layer of the skin) on glabrous skin, resulting in a greater thermal insulation of this type of skin, contributes to the reduced thermal conductance of the finger pad (Rushmer et al. 1966) and therefore to the lower thermosensitivity of glabrous as opposed to hairy skin during short-contact cooling and/or heating, as a result of the longer time that is needed for a given change in temperature of glabrous skin superficial layers to penetrate to the underlying tissues (e.g., stratum granulosum) where the thermoreceptors lie (McGlone and Reilly 2010). In this context, as thermal sensitivity seems to play the key role in sensing wetness, it is therefore reasonable to hypothesize that, despite a larger content in highly spatially sensitive mechanoreceptive afferents (Abaira and Ginty 2013) that could potentially contribute to an increase in the haptic perception of wetness, the lower thermal sensitivity of the glabrous skin might translate to the palms of the hands being generally less sensitive to wetness than the rest of the body.

From a thermoregulatory standpoint, this could be supported by the fact that, as opposed to regions covered by hairy skin, human hands are indeed more of a specialized organ for heat exchange than a thermosensory organ (Romanowsky 2014). Finally, from a behavioral point of view, the fact that hairy skin presents a higher sweat production than glabrous skin (for thermoregulatory reasons) (Smith and Havelin 2012) could result in individuals expecting to experience cutaneous wetness in larger magnitude on hairy than on glabrous skin sites.

Further support for the hypothesis of a possible neural representation of a “typical wet stimulus” being based primarily on cold and mechanosensory A-type afferents could be found when looking at the perceptions evoked by the skin’s contact with cold moisture (Fig. 6, G and H). In the case of the skin’s contact with cold moisture (i.e., temperature below $T_{sk}$), Aδ-nerve fibers (subserving cold sensitivity) and Aβ-nerve fibers (subserving light touch) are involved in the somatosensation of moisture. In this scenario, as both Aδ and Aβ afferents are available within the processing pathway we suggest to subserve wetness, the extent of perceived wetness will be greater compared with the wetness experienced when in contact with warm and neutral moisture. In this study we observed that although all the stimuli had the same moisture levels, cold-wet stimuli were sensed as significantly wetter than warm-wet and neutral-wet stimuli, particularly during the static interaction, when only thermal cues were available (Fig. 6G). Also, the selective block trials indicated that the extent of perceived wetness was overall significantly decreased, mainly because of the reduced cutaneous cold sensitivity and mechanosensitivity.

The critical role of experiencing coldness in the ability to sense wetness is in line with our previous findings. We have recently demonstrated that an illusion of local skin wetness can be evoked during the skin’s contact with a cold-dry surface producing skin cooling rates in a range of 0.14 – 0.41°C/s (Filingeri et al. 2013, 2014a, 2014b), a temperature course that is similar to that suggested to occur when the skin is physically wet (Daanen 2009). Evidence in support of the role played by thermal cold afferents in sensing wetness comes from studies investigating the role of cold-sensitive neurons in ocular dryness and wetness (Belmonte and Gallar 2011; Hirata and Oshinsky 2012). Hirata and Oshinsky (2012) have recently suggested that the sensation of “ocular wetness” could be based on the afferent activity of corneal cold-sensitive neurons, carrying a sensation of gentle cooling via a transient receptor potential (TRP) channel activation. The authors proposed this as a potential explanation for why tears on the ocular surface could feel wet (Hirata and Oshinsky 2012). The possibility that cold-sensitive neurons and TRP channels could be critical determinants of the human ability to sense wetness represents an intriguing possibility (Montell 2008), particularly as TRP channels have been shown previously to be required for hygro-sensation and detection of both dry and moist air in some insects, such as the fruit fly *Drosophila melanogaster* (Liu et al. 2007). However, the speculative nature of this hypothesis highlights the need for further experimental evidence in order to better understand the still little investigated neurophysiological mechanisms involved in such complex cognitive functions such as wetness sensitivity. For example, it must be stressed that on the basis of the present results it cannot be concluded that coldness alone (without tactile component) is sufficient for generating a perception of wetness. Although we believe that a perception of wetness always results from the combination of thermal and tactile cues (and in this respect, our proposed processing model provides evidence in support of which cues the central nervous system relies on more in its prediction of wetness) (Ernst and Banks 2002), further research should deal with, e.g., whether wetness could be evoked without any tactile component (e.g., through radiative cooling) or whether tactile stimuli only can evoke wetness, in order to further our understanding of somatosensation in the context of perceptual inference.

It deserves mention that C-nerve fibers (i.e., polymodal afferents responding to nociceptive, warm, cool, and light mechanical stimulation with conduction velocities ranging from 0.2 to 2 m/s) (McGlone et al. 2014) have been shown previously to respond to innocuous cold temperatures (Campiero et al. 2001) as well as to touch (Lumpkin and Caterina 2007). Therefore, it might be argued that these fibers could also contribute to the sensory processing of skin wetness. However, as their contribution to conscious cold sensations has not been proven conclusively (Schepers and Ringkamp 2010) (therefore suggesting an alternative autonomic thermoregulatory function) and as their mechanical sensitivity seems to be specifically tuned to affective as opposed to discriminative touch (Løkken et al. 2009; Olausson et al. 2010), the contribution of C-nerve fibers to the perception of wetness seemed not to be critical, at least not within the experimental conditions of the present study. Indeed, we observed that the reduction in A-nerve fiber afferent activity, when either naturally (i.e., static contact with warm and neutral moisture) or artificially (i.e., during the compression ischemia protocol) induced, was sufficient to significantly change the dynamic of the perception of wetness (i.e., significantly diminishing the extent of perceived skin wetness). Nevertheless, because of the polymodal nature of these nerve fibers (McGlone et al. 2014) and because of the absence of a direct measurement of peripheral neural activity in
the present study (e.g., by microneurographic recording), the hypothesis of C fibers significantly contributing to the sensory integration of skin wetness cannot be ruled out conclusively.

In summary, a neurophysiological model of cutaneous wetness sensitivity, based on the multimodal transformation of A-type somatosensory afferents, was developed in order to explain how humans could sense warm, neutral, and cold cutaneous wetness. This model supports the hypothesis that the brain infers about the perception of wetness in a rational fashion, taking into account the variance associated with thermal afferents and mechanoreceptors evoked by the contact with wet stimuli, and comparing this with a potential neural representation of a “typical wet stimulus,” which is based on prior sensory experience. In this respect, our findings have both a fundamental and a clinical significance. They provide insights on the integration and processing of somatosensory information occurring between peripheral and central nervous systems. Also, they provide insights on the possible origin of symptoms such as spontaneous sensations of cold wetness experienced across the body by individuals suffering from multiple sclerosis or neuropathies (Hulse et al. 2010; Nolano et al. 2008; Rae-Grant et al. 1999; Susser et al. 1999). As these disorders have been shown to affect peripheral A-nerve fiber functions and to alter somatic perception, the neurophysiological model of cutaneous wetness sensitivity developed in this study could be used as a frame of reference for normal and altered somatosensory function.

DISCLOSURES

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AUTHOR CONTRIBUTIONS

Author contributions: D. Filingeri, D. Fournet, S.H., and G.H. conception and design of research; D. Filingeri performed experiments; D. Filingeri analyzed data; D. Filingeri and G.H. interpreted results of experiments; D. Filingeri prepared and revising the manuscript. Loughborough University and Oxylane Research provided financial support.

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