

# Coding of pleasant touch by unmyelinated afferents in humans

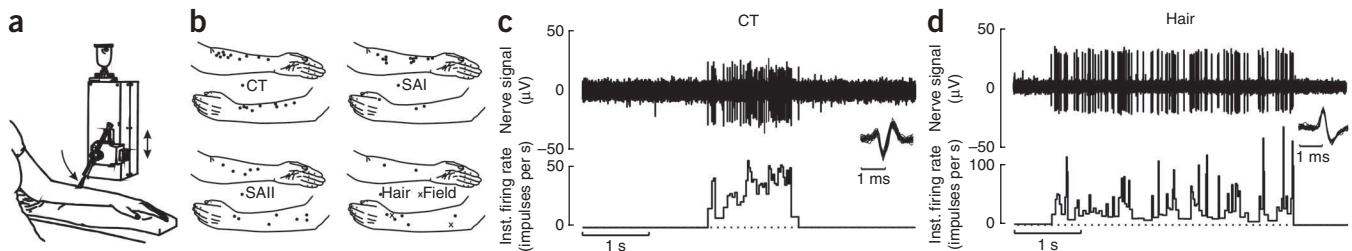
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**Pleasant touch sensations may begin with neural coding in the periphery by specific afferents. We found that during soft brush stroking, low-threshold unmyelinated mechanoreceptors (C-tactile), but not myelinated afferents, responded most vigorously at intermediate brushing velocities (1–10 cm s<sup>-1</sup>), which were perceived by subjects as being the most pleasant. Our results indicate that C-tactile afferents constitute a privileged peripheral pathway for pleasant tactile stimulation that is likely to signal affiliative social body contact.**

Although the neurobiology of pleasure has been described from a CNS perspective<sup>1,2</sup>, the contribution of the peripheral nervous system has received little attention. In contrast, unpleasant somatosensations are well-characterized in terms of peripheral afferent signaling in dedicated nociceptive afferents<sup>3,4</sup>. We asked whether pleasant tactile sensations are coded for by specialized peripheral tactile afferents, analogous to pain sensations. A subclass of unmyelinated afferents (C-tactile) provided us with a candidate for such a specific role in mediating pleasant touch. They respond vigorously to slow and light stroking<sup>5,6</sup> and are found only in hairy skin<sup>6,7</sup>. C-tactile afferents follow ascending pathways that are distinct from those of myelinated tactile fibers. Selective C-tactile stimulation activates the left anterior insular cortex<sup>8</sup>, an area that has been implicated in the processing of positive emotional feelings<sup>9,10</sup>.

After obtaining informed written consent, we used a microneurography technique for recording single afferent activity in awake humans and used a robotic device to deliver moving tactile stimuli (**Supplementary Methods** online). We recorded from single afferents in the hairy skin of the forearm responding to innocuous touch (C-tactile,  $n = 20$ ; slowly adapting type I (SAI),  $n = 15$ ; slowly adapting type II (SAII),  $n = 12$ ; hair,  $n = 7$ ; field,  $n = 2$ ; **Fig. 1**). We stimulated each unit with a soft brush moving at a constant speed over the receptive field using two different normal forces (0.2 and 0.4 N; **Supplementary Fig. 1** online). An average of 43 brushing stimuli (range 8–64) was applied to each unit.

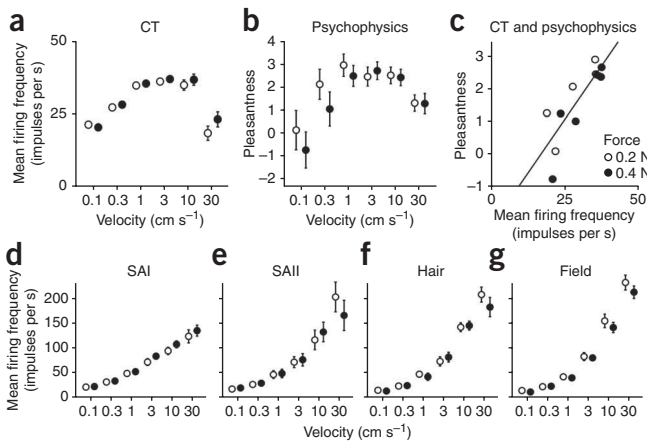
The total numbers of spikes that were elicited by brush stroking were similar for C-tactile, SAI, SAI and hair units, whereas field units responded with fewer impulses (Kruskal-Wallis,  $P < 0.0001$ ; Dunnett T3 *post hoc* tests,  $P < 0.0001$ – $0.002$ ; **Supplementary Fig. 2** online). The relationship between brush-stroking velocity and firing rate was distinctly different between C-tactile and myelinated afferents (**Fig. 2**). C-tactile afferents showed an inverted U-shaped relationship between brushing velocity and mean firing rate (derived from the interspike intervals) with highest responses at 1, 3 and 10 cm s<sup>-1</sup> (**Fig. 2a** and **Supplementary Fig. 3** online). In contrast, mean firing increased monotonically with brushing velocity in all myelinated afferent types (**Fig. 2d–g**). In C-tactile afferents, a negative quadratic regression model provided a better fit than a linear model in 14 of the 16 units that were explored with the full range of velocities (F test,  $P = 0.05$  or less; mean  $R^2 = 0.44$ , range = 0.29–0.60; **Supplementary Table 1** online). The peak of the fitted quadratic curve was at 2.1 cm s<sup>-1</sup>. In myelinated units, on the other hand, a positive, rather than a negative, quadratic regression model provided an improved fit in 11 units (mean  $R^2 = 0.93$ , range = 0.77–0.99) and the fit was better for a linear model in six units (mean  $R^2 = 0.57$ , range = 0.43–0.71). Maximum firing rate showed a similar dependency on the brushing velocity as mean firing rate in all five unit types. The indentation force had no



**Figure 1** Brush stimulation and nerve recordings. **(a)** Robotic tactile stimulator, developed at the University of North Carolina Chapel Hill and by Dancer Design, for soft brush stroking with well-controlled velocity and force. **(b)** Location of the receptive field for each unit ( $n = 56$ ). Brush stroking was applied over the receptive field center, perpendicular to the skin. CT, C-tactile. **(c,d)** Nerve response and interspike interval histogram for a C-tactile afferent **(c)** and a hair afferent **(d)** to soft brush stroking with a velocity of 3 cm s<sup>-1</sup> and calibrated normal force of 0.4 N. Individual nerve spikes are superimposed on an expanded time scale below the nerve recording to illustrate differences in impulse shape between unmyelinated and myelinated afferents. Note that scaling on the interval histogram is different in **c** and **d**.

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**Figure 2** Neural discharge rate and perception of pleasantness in response to soft brush stroking. (**a,d–g**) Dots show average discharge rates during brush stroking for the different types of mechano-afferents explored with the full range of stimulus velocities (C-tactile,  $n = 16$ ; SAI,  $n = 8$ ; SAIL,  $n = 3$ ; hair,  $n = 4$ ; field,  $n = 2$ ; see **Supplementary Fig. 3** for examples of single-unit data). Note that scaling on the y axes is different for C-tactile and myelinated afferents. (**b**) Average ratings of perceived pleasantness in response to soft brush stroking. Data are from ten subjects. (**c**) Ratings of pleasantness as a function of neural discharge rate in C-tactile afferents. Mean pleasantness ratings are plotted against the corresponding mean firing frequency for each brushing velocity and force. The plot is based on the data shown in **a** and **b**. The linear correlation was significant (Pearson's linear regression,  $R^2 = 0.70$ ,  $P = 0.00063$ ). Error bars indicate s.e.m.

consistent effect except for SAI units that responded with higher frequency at the higher calibrated force (**Fig. 2d**).

In a separate session, ten subjects rated the positive hedonic quality<sup>1</sup> of the brush stroking on a visual-analog scale (VAS; **Fig. 2b** and **Supplementary Methods and Discussion** online). Regression analysis of brush velocity and VAS scores showed that a negative quadratic regressor provided a better fit than a linear regressor (F test,  $P = 0.036$ ). Subjects rated 1, 3 and 10  $\text{cm s}^{-1}$  as being most pleasant and the peak of the fitted quadratic curve was at 2.8  $\text{cm s}^{-1}$ .

The similar stimulation protocol in the microneurography and psychophysical sessions allowed us to compare the average discharge rate, estimated from a population of single units, with the average hedonic rating, estimated from a population of subjects<sup>3,4,11</sup>. There was a significant linear correlation between mean firing rates and mean ratings of pleasantness for C-tactile units (Pearson's linear regression,  $R^2 = 0.70$ ,  $P = 0.00063$ ; **Fig. 2c**) but not for myelinated units (SAI,  $R^2 = 0.12$ ; SAIL,  $R^2 = 0.04$ ; hair,  $R^2 = 0.06$ ; field,  $R^2 = 0.04$ ).

Because C-tactile afferents are found in forearm, but not glabrous palm skin, we compared pleasantness ratings of brush stroking in these two skin areas in another ten subjects (**Supplementary Methods**). VAS ratings for pleasantness were significantly lower in the palm (two-way within-subjects ANOVA,  $P = 0.0001$ ; **Supplementary Fig. 4** online). This difference was most pronounced at 3  $\text{cm s}^{-1}$  (one-way within-subjects ANOVA, Bonferroni corrected,  $P = 0.0006$ ), which coincides with the optimal stimulus velocity for C-tactile afferents. In the palm, there was no robust relationship between brush velocity and pleasantness ratings, as neither the linear nor the quadratic regressors were significant (F test,  $P = 0.44$  and  $0.43$ ).

These results are, to the best of our knowledge, the first demonstration of a relationship between positive hedonic sensation and coding at the level of the peripheral afferent nerve, suggesting that C-tactile fibers contribute critically to pleasant touch. Soft brush stroking on hairy skin was perceived as most pleasant when it was delivered at velocities that were most effective at activating C-tactile afferents (1–10  $\text{cm s}^{-1}$ ), with a linear correlation between C-tactile impulse frequency and pleasantness ratings. In contrast, the response of myelinated afferents increased with faster velocities (30  $\text{cm s}^{-1}$ ) and showed no relationship with pleasantness ratings. The sweep of the brush over the skin surface activates a large number of tactile afferents and discharge of any given single unit is not sufficient for a pleasant percept<sup>6</sup>. However, of all of the unit types tested, only the C-tactile afferent firing pattern correlated with average psychophysical ratings. In the palm, which lacks C-tactile afferents, we found no relationship between brush velocity and pleasantness ratings (see also **Supplementary Discussion**). The variance of mean C-tactile impulse firing frequency could explain as much as 70% of the variance

in the pleasantness ratings ( $R^2 = 0.70$ ). Indeed, C-tactile input for brush stroking is substantial: microneurography recordings demonstrate that C-tactile afferents are encountered roughly as often as myelinated units<sup>6</sup> and the number of impulses evoked by brush stroking was similar for the two afferent types, despite lower discharge rates for C-tactile afferents. Nevertheless, hedonic ratings probably depend not only on bottom-up neural signaling but also on top-down factors related to context, previous experience, expectation, homeostatic state of the individual and culture<sup>1,12</sup>. Selective C-tactile stimulation evokes a sympathetic skin response that is consistent with affective modulation<sup>13</sup> and C-tactile fibers project to insular cortex, a site of emotional processing and interoceptive awareness<sup>8,10</sup>. Considering these properties alongside our findings, we propose that C-tactile processing is tuned to slow, gentle tactile stimulation that probably occurs during close affiliative interactions with conspecifics<sup>12,14,15</sup>, perhaps especially between mothers and infants. Such tactile interaction may be distinct from sexual function and C-tactile receptors have not been found in genitalia<sup>7</sup>. A system of C-tactile afferents, projecting to insular cortex, may thus constitute a privileged peripheral pathway for gentle, pleasant tactile stimulation of a social nature.

*Note: Supplementary information is available on the Nature Neuroscience website.*

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#### AUTHOR CONTRIBUTIONS

L.S.L., J.W., F.M. and H.O. designed the study. L.S.L. and J.W. carried out the microneurography experiments and analyzed the data. L.S.L. performed the psychophysical experiments. L.S.L., J.W., I.M. and H.O. wrote the paper. F.M. coordinated the construction of the robotic tactile stimulator.

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