Title
Aβ-CT Affective Touch: Touch Pleasantness Ratings for Gentle Stroking and Deep Pressure Exhibit Dependence on A-Fibers

Permalink
https://escholarship.org/uc/item/7q0270gf

Journal
eNeuro, 10(5)

ISSN
2373-2822

Authors
Case, Laura K
Madian, Nicholas
McCall, Micaela V
et al.

Publication Date
2023-05-01

DOI
10.1523/eneuro.0504-22.2023

Aβ-CT affective touch: Touch pleasantness ratings for gentle stroking and deep pressure exhibit dependence on A-fibers

Abbreviated title: A-fibers required for gentle and deep touch pleasantness

Laura K. Case[1,2], Nicholas Madian[2], Micaela V McCall[2], Megan L Bradson[2], Jaquette Liljencrantz[2,3], Benjamin Goldstein[1], Vincent J Alasha[1], & Marisa S Zimmerman[1]

1 Department of Anesthesiology, UC San Diego School of Medicine, CA, USA, 92037
2 National Center for Complementary and Integrative Health, NIH, Bethesda, MD, USA, 20892
3 Department of Anesthesiology and Intensive Care, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

Corresponding author: Laura K. Case lcase@health.ucsd.edu

Author contributions

LC and JL Designed Research; NM, MM, MB, BG, VA, and MZ Performed Research; LC, NM, VA, and MZ analyzed data; LC Wrote the paper

Number of figures: 4
Number of tables: 1
Words in Abstract: 199
Words in Significance Statement: 111
Words in Introduction: 914
Words in Discussion: 1046

Acknowledgements

We are indebted to Catherine Bushnell for her mentorship and supervision at NCCIH, and her input into the study design. We are also deeply grateful to the clinicians and staff at NCCIH for assistance in conducting Study 1. Additionally, we are grateful to Dr. Olausson for the use of his custom-built vibration devices.

Conflict of Interest

Authors report no conflict of interest.

Funding Sources

The project described was partially supported by the National Institutes of Health, Grant UL1TR001442, the Intramural Research program of the National Center for Complementary and Integrative Health (NCCIH)–National Institutes of Health, and NCCIH Grant R00-AT009466. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Abstract

Gentle stroking of the skin is a common social touch behavior with positive affective consequences. A preference for slow versus fast stroking of hairy skin has been closely linked to the firing of unmyelinated C-tactile (CT) somatosensory afferents. Because the firing of CT afferents strongly correlates with touch pleasantness, the CT pathway has been considered a social-affective sensory pathway. Recently, ablation of the spinothalamic pathway- thought to convey all C-fiber sensations- in patients with cancer pain impaired pain, temperature, and itch, but *not* ratings of pleasant touch. This suggested integration of afferent A and CT fiber input in the spinal cord, or mechanoreceptive A-fiber contributions to computations of touch pleasantness in the brain. However, contribution of mechanoreceptive A-fibers to touch pleasantness- in humans *without* pain- remains unknown. In the current, single-blinded study we performed two types of peripheral nerve blocks in healthy adults to temporarily eliminate the contribution of A-fibers to touch perception. Our findings show that when mechanoreceptive A-fiber function is greatly diminished, the perceived intensity *and* pleasantness of both gentle stroking and deep pressure are nearly abolished. These findings demonstrate that explicit perception of the pleasantness of CT-targeted brushing and pressure both critically depend on afferent A-fibers.

Key Words: somatosensory, C-tactile; pleasant touch; gentle brushing; nerve block; deep pressure, A-beta

Significance Statement: In the current study we performed two types of peripheral nerve blocks in healthy adults to temporarily eliminate the contribution of A-fiber afferents to touch perception. We show that when afferent A-fiber function is greatly diminished, the perceived intensity *and* pleasantness of gentle stroking are nearly abolished. These findings demonstrate for the first time that explicit perception of the pleasantness of C-tactile (CT)-targeted touch critically depends upon A-fiber afferents. In addition, we show the same outcome for deep pressure (similar to hugs and massage), another form of social-affective touch we have previously validated in the lab. Together these findings demonstrate that social touch is not conveyed solely by the CT pathway.

Introduction

While top-down effects of mood and social context strongly shape the affective nature of touch(Sailer and Leknes 2022), there is evidence that bottom-up sensory afferents prime the affective valence of pleasant touch, much as stimulation of nociceptors frequently leads to pain. Conventionally, myelinated Aα and Aβ afferents convey proprioceptive and touch signals, while thinly myelinated Aδ and unmyelinated C-fibers relay temperature, chemical, and pain signals(Burgess and Perl 1967). However, the pleasantness of gentle stroking has been linked to a subset of C-fibers called C-tactile (CT) afferents, which are maximally activated by slow gentle stroking(Vallbo, Olausson et al. 1999). The firing of CT fibers correlates with ratings of the pleasantness of gentle stroking(Löken, Wessberg et al. 2009), and CT touch activates the posterior insula(Olausson, Lamarre et al. 2002) and increases positive affect(Pawling, Trotter et al. 2017). Given their affective effects and anatomical distinction from the Aβ pathway, it is argued that CT fibers subserve a distinct social-affective pathway described in the "Social Touch Hypothesis" (Vallbo, Olausson et al. 1999, Morrison, Loken et al. 2010), while afferent A-beta fibers predominantly support discriminative aspects of touch(McGlone, Vallbo et al. 2007, Olausson, Cole et al. 2008, Morrison, Loken et al. 2010, Gordon, Voos et al. 2013).

Affirming the role of CT fibers in touch pleasantness, patients with hereditary reductions in C-fiber afference exhibit reduced preference for slow stroking(Morrison, Löken et al. 2011), while patients with A-fiber deafferentation report mild pleasantness of CT-targeted touch and show CT touch-induced insula response(Olausson, Lamarre et al. 2002, Olausson, Cole et al. 2008). Patients with a functional loss of the *PIEZO2* ion channel subserving mechanotransduction, who exhibit severe tactile deficits, similarly remain able to detect CT-targeted slow stroking on hairy skin (Chesler, Szczot et al. 2016). However, these results stem from small studies of patients with rare sensory abnormalities or disease, who may have abnormal sensory development or compensatory brain plasticity.

There is also evidence that pleasant touch perception may require convergent A- and C-fiber inputs. This was postulated early in the CT theory (summary in(AB Vallbo 2009)), and recent findings contribute positive evidence. First, in rodents, some Aβ and CT afferents converge onto common interneurons in the spinal cord(Abraira, Kuehn et al. 2017). Second, in humans with intractable unilateral cancer-related pain, ablation of the lamina I-spinothalamic pathway—the putative pathway for all unmyelinated afferents—largely eliminates perception of pain, temperature, and itch, but does not eliminate the pleasantness of slow stroking(Marshall, Sharma et al. 2019). Finally, electroencephalography (EEG) recordings demonstrate modulation of primary somatosensory cortex by gentle stroking temporally preceding the slower CT signal, and correlated with touch pleasantness ratings, suggesting CT modulation of dorsal column (Aβ-associated) spinal projections (Schirmer, Lai et al. 2022), while magnetoencephalography (MEG) recordings show activation of more affective brain areas such as the insula and cingulate by A-fibers during naturalistic stroking (Hagberg, Ackerley et al. 2019). Indeed, it has been hypothesized that stimulation of CT afferents might act as positive reinforcement for gentle tactile interaction in the social development of infants(Ackerley 2022, Croy, Fairhurst et al. 2022).

Furthermore, gentle stroking on the glabrous skin of the palm, where CT fibers are scarce(Watkins, Dione et al. 2021), still elicits (slightly lower) ratings of conscious pleasantness(Loken, Evert et al. 2011, Klöcker, Arnould et al. 2012, Cruciani, Zanini et al. 2021). Together with the aforementioned findings, this result suggests a potential critical role of A-beta mechanoreceptive afferents in pleasant touch perception- however, the contribution of the scarce CTs is not known. In sum, it is not known whether A-beta mechanoreceptive afferents are required for pleasant touch perception in the moment of touch, in healthy humans, or whether CT fibers can be sufficient.

In addition to the pleasant effects of gentle stroking, our research also confirms the pleasant and relaxing effects of deep pressure, as in massage(Case, Liljencrantz et al. 2020). However, the mechanism for this sensation is not known. In humans, cutaneous anesthetic block eliminates skin sensation with little alteration in the sensation of deep pressure(Graven-Nielsen, Mense et al. 2004), suggesting distinct pathways for deeper pressure sensation. Indeed, nerve compression blocks first block cutaneous sensation, then deep pressure, and finally deep pressure pain(Kellgren 1948), and animal research has shown that both myelinated and unmyelinated sensory afferents in muscle can respond to pressure(Kaufman, Longhurst et al. 1983, Mense and Meyer 1985, Abrahams 1986, Lewin and McMahon 1991). Consistent with these findings, our human research has shown the dependence of pressure intensity sensing on Aβ afferents, with a non-*Piezo2* mechanism for mechanotransduction(Case, Liljencrantz et al. 2021). However, the neural mechanisms for pleasantness perception has not been studied.

Here, we conduct two types of temporary A-fiber blockades to determine the contribution of mechanoreceptive A-fiber afferents to conscious perception of the pleasantness of gentle stroking and deep pressure, at the time of touch. Ischemic nerve block (Study 1) yields clear separation of A- and C-fiber functions(Laursen, Graven-Nielsen et al. 1999) for a large area of skin, but causes pain and discomfort. Nerve compression block (Study 2) affects a smaller skin surface area, but with minimal discomfort- and has previously been used to correlate specific nerve afferents with sensory percepts(Wahren, Torebjörk et al. 1989, Wasner, Schattschneider et al. 2004, Forstenpointner, Binder et al. 2019). Furthermore, the latter technique has demonstrated preferential blockade of A-fibers during microneurography recordings in humans(Torebjörk and Hallin 1973, Mackenzie, Burke et al. 1975). These nerve block techniques offer complementary strengths and weaknesses that together afford a robust test of the contribution of afferent A-fibers to affective qualities of touch, in the moment of touch.

Materials and Methods

Study 1:

Participants:

Study 1 was approved by the National Institutes of Health Intramural Institutional Review Board. This study was a preliminary study and no sample size calculation was performed. Healthy controls were selected based on age and sex from participants in a broad screening protocol at NCCIH. Potential participants were scheduled for a telephone screening during which the study procedures were described, and eligibility criteria were reviewed. Participants underwent medical screening and were excluded if they had unstable medical or psychiatric conditions and any abnormalities of the skin or nerves. All participants provided informed consent and were financially compensated for their time. A total of 7 healthy volunteers participated; complete data with successful separation of A- and C-fiber nerve function was obtained and analyzed from 5 participants (2 female and 3 male, ages 21-25).

Methods:

Baseline affective touch task: At baseline each participant received gentle brushing (back of the hand at a rate of 3 cm/s for 15s using a soft goat hair watercolor brush, **Figure 1a**). Participants rated each of these stimuli on two visual analog scales- one for intensity (anchors of "no sensation" (coded as 0) to "highest possible intensity" (coded as 100)) and one for pleasant/unpleasantness (anchors "extremely unpleasant" (-100) to "neutral" (0) to "extremely pleasant" (100)). Participants then received oscillating deep pressure from a commercially available hand massager (Daiwa Felicity – Acu Palm Hand Massager, Model No. USJ-881; **Figure 1b)** for 20s, and rated it on the same intensity and pleasant/unpleasantness scales. The massager had three pre-set patterns and each participant sampled them and selected the most pleasant to use at the beginning of the study. All patterns administered very deep pressure between the wrist and to of the hand, but force and frequency information were not provided by the manufacturer. Testing was conducted on the arm to be blocked and then on the control arm.

Nerve block placement: The participant's left arm (this was the non-dominant arm for 3 of 5 participants) was elevated above the head and exsanguinated for about 1 minute. Then, an automated blood pressure cuff device was wrapped around the brachium of the arm and was rapidly inflated to approximately 100mmHg above the participant's systolic blood pressure. The arm was then rested on a pillow with the dorsal side down. Vital signs were monitored at regular intervals.

Nerve function monitoring: We started with four baseline rounds of testing, which included tests of several different sensory stimuli that have known associations with specific afferents. To track Aβ function we used a custom vibration device that applied 200Hz vibration for a random interval of 1-6s on a 1.3 x 4 cm region of skin on the lower palm near the wrist using a custom-built probe (4.0 cm x 1.2cm x 0.7cm of balsa wood connected to a piezo-element (Piezo Systems, Inc., Cambridge, MA, USA; previously used in (Liljencrantz, Strigo et al. 2017)) (**Figure 1c)**. Participants reported the onset and offset of vibration verbally over a set of three trials. To track C-fiber function we applied a Medoc thermode (Medoc, Ramat Yishay, Israel) (**Figure 1d)** over the ventral forearm at 32°C, and increased the temperature at a rate of 1°C/s until the participants indicated perception of warmth by a button press. Additional somatosensory tasks for other purposes were conducted that are not reported here. The vibration and warmth threshold tasks were repeated approximately every 2 minutes until a substantial loss of vibration detection (<50% detection) was observed.

Figure 1 here

Final affective testing: the baseline affective touch task was repeated directly after loss of vibration perception.

During all testing the participants wore noise-isolating headphones playing white noise and had a visual barrier obscuring their vision of the stimuli.

Study 2:

We initiated Study 2 to overcome limitations of Study 1, particularly the painful and aversive nature of the ischemic nerve block. Study 2 was preregistered with the Open Science Framework, doi https://osf.io/q2b68.

Participants:

Study 2 was approved by the UC San Diego Biomedical Institutional Review Board. Given the Cohen's *d effect sizes of* 1.3 and 1.6 in Study 1, and assuming a within-subject correlation of 0.5 and an attrition rate of 35%, a sample size of 24 was proposed to provide more than 0.8 power to detect an effect size of at least $d = 0.8$ with a two-sided $\alpha = 0.05$. Healthy controls were recruited from the local university and community, and from previous studies. Potential participants were scheduled for a telephone screening during which the study procedures were described, and eligibility criteria were reviewed. Participants were included if they were 18-50 years of age, right-handed, fluent in English, and had no indication of chronic pain or current pain. Participants were excluded if they had BMI >40, unstable psychiatric conditions, current opiate use or pregnancy (urine drug screen), current lactation, history of fainting from medical procedures, allergies to latex, major medical conditions, sensory or motor abnormalities, coagulopathy or use of anti-coagulant medications, inability to communicate with investigator or rate sensations, nerve block site infection or injury, or any other medical counterindications to nerve block. All participants provided informed consent and were financially compensated for their time. A total of 24 healthy volunteers participated (7 male and 17 female; ages 20-50; self-reported ethnicity 5 White, 5 Hispanic, 6 Asian, 1 mixed; $M = 26.8$, $SD = 7.64$). There was no overlap in participants between Studies 1 and 2.

Methods:

Participants completed a urine pregnancy test and opiate drug test.

Perception of affective touch (*Brushing Rating Task* and *Pressure Rating Task*) was tested before and after the nerve block took effect, first on the blocked arm and then on the control arm. All testing was conducted within the region of the dorsal hand affected by the compression block.

Brushing Rating Task: First, gentle brushing (**Figure 2a**) was administered sequentially to the blocked and control arm for 15s each, using the side of a goat hair watercolor brush (<1cm). At the end of each brushing period, participants made ratings on two visual analog scales of intensity (anchors of "no sensation" (later coded as 0) to "highest possible intensity" (100)) and pleasant/unpleasantness (anchors "extremely unpleasant" (later coded as -100) to "neutral" (0) to "extremely pleasant" (100)).

Pressure Rating Task: Deep pressure was administered to the blocked and control arm for 15s each using a handheld rolling massage ball (**Figure 2b**), applied by the experimenter to the dorsal area of the hand between the thumb and pointer finger. The massage ball was rolled across the area repeatedly in a proximal to distal direction at a slow velocity similar to the brushing velocity and an approximate force of 1-1.2N. Participants rated intensity and pleasant/unpleasantness as in the *Brushing Rating Task.*

Baseline Nerve Function Tasks: Cold detection, vibration detection, and warmth detection were assessed at baseline, before placement of the nerve block. Each task was comprised of three trials and the mean of the three trials was taken to establish baseline sensory function. The same vibration task was used as in Study 1, but vibration was applied to the dorsal hand (**Figure 2c**). In the cold detection task, a QST.Lab T09 thermode (QST.Lab, Strasbourg, France) was placed on the dorsal hand in the area anticipated to be blocked (**Figure 2d**). The thermode started at the participant's skin temperature and was lowered at a rate of 2°C/s until the participant indicated their perception of a cooling sensation via a response button. In the warmth detection task, the thermode was placed on the dorsal hand and increased at a rate of 2°C/s until the participant indicated their perception of a warming sensation.

The *Brushing Rating Task, Pressure Rating Task,* and *Baseline Nerve Function Tasks* were each conducted a second time to provide familiarization and comfort with the tasks prior to nerve block placement.

Nerve Block Placement: We initiated a nerve compression block over the left superficial radial nerve following validated procedures(Ziegler, Magerl et al. 1999, Nahra and Plaghki 2003, Forstenpointner, Binder et al. 2019): while the left hand rested in semi-prone position, a ~1-inch cloth tourniquet was placed over the left forearm about 7cm from the wrist. A 5-lb weight was dangled from the tourniquet, similar to the weights used in some nerve compression studies(Wahren, Torebjörk et al. 1989) (see **Figure 2**). This technique often takes an hour to achieve loss of touch and cold perception(Nahra and Plaghki 2003), but does not affect major blood vessels or induce significant pain(Wasner, Schattschneider et al. 2004). The block was released within a common safety time window of 90min for healthy research participants(Forstenpointner, Binder et al. 2019).

Nerve Function Monitoring: After block placement, cold and warm detection thresholds were monitored every ~5 minutes following the same procedure as at baseline. The first two rounds of monitoring were used to establish baseline sensory nerve function. The function of Aβ fibers was monitored by the vibration task and cold threshold, with a loss of A-beta mechanoreceptive afferents function determined by vibration perception <50% (as in our previous study (Case, Liljencrantz et al. 2021)), and a drop in cold threshold of >5°C. The anesthetic zone was monitored with a cotton swab, given variability in distribution of the superficial radial nerve(Keplinger, Marhofer et al. 2018), and stimulus placement was adjusted accordingly. The continued function of C-fibers was confirmed by warm thresholds maintained within 1°C of baseline(Wahren, Torebjörk et al. 1989).

Figure 2 here

Post-Block Affective Touch Testing: The *Brushing Ratings Task* and *Pressure Rating Task* were repeated directly after the loss of vibration and cold detection.

Final Nerve Function Confirmation: After the nerve block was achieved and the affective touch testing was completed, a final round of nerve function testing was conducted to confirm maintained loss of A-fiber sensation and preservation of C-fiber function.

Upon completion of all test procedures *or* upon reaching the 90min safety limit, the tourniquet was removed, and sensory function was quickly restored to baseline.

Data analysis: Study 1 was a preliminary study with lower power. We conducted paired t-tests to compare ratings of pleasantness and intensity before versus after nerve block. In Study 2, we conducted linear mixed effect analyses using pleasantness and intensity as dependent measures, time, arm, and their interaction as fixed effects, and participant intercept and slopes as random effects.

Results

Study 1

The ischemic compression block successfully separated A- and C- fiber function in the 5 participants we report data from (of the 2 participants not analyzed here, 1 reported intolerable pain and 1 lost the ability to detect heat before vibration detection was affected). By around 20 minutes, vibration detection dropped from 100% to 0 in 4/ 5 participants, and 50% in the 5th, while heat detection thresholds remained unaffected (<1°C change in 4 subjects, <2°C in 1). At that point in time, ratings of both intensity (previously reported in (Case, Liljencrantz et al. 2021)) and pleasantness were nearly eliminated for both brushing (**Figure 3**) and pressure (**Figure 4**), but were largely unchanged in the control arm. Compared to baseline, nerve block reduced the pleasantness of both gentle brushing (blocked arm PRE $M = 43.6$, $SD = 30.6$, POST $M = 3.4$, $SD = 6.5$; control arm PRE $M = 43.8$, $SD = 32.5$, POST $M = 16.0$, $SD = 14.6$; $t(4) = 3.2$, $p = 0.03$, Cohen's $d = 0.55$; Table 1 line a) and deep pressure (blocked arm PRE $M = 19.2$, $SD = 20.0$, POST $M = 0.4$, $SD = 0.9$; control arm PRE $M = 18.6$, $SD = 21.2$, POST $M = 11.2$, $SD = 13.4$, trend; $t(4) = 2.2$, $p = 0.09$, Cohen's $d = 0.91$; Table 1 line b), as well as their intensity (gentle brushing blocked arm PRE $M = 24.8$, $SD = 21.5$, POST $M = 3.6$, $SD = 4.6$; control arm PRE $M = 27.8$, $SD = 17.5$, POST $M = 25.2$, $SD = 19.0$, trend, $t(4) = 2.1$, $p = 0.1$, Cohen's $d = 1.6$; Table 1 line c; deep pressure blocked arm PRE $M = 40.4$, $SD = 21.5$, POST $M = 3.2$, $SD = 7.2$; control arm PRE $M = 42.8$, $SD = 24.7$, POST $M = 30.6$, $SD = 18.4$, $t(4) = 3.3$, $p = 0.03$, Cohen's $d = 1.7$; Table 1 line d).

Study 2

The nerve compression block successfully separated A- and C-fiber function in 17 of the 24 study participants. Seven additional subjects were dismissed from their sessions (5 reached the time limit without successful fiber separation, 1 reported intolerable pain, and 1 experienced abnormal nerve tingling prior to nerve block) and thus are not analyzed here. At about 1 hour ($M = 52.06$ min), vibration detection dropped below 50% in all 17 of the analyzed participants (and was maintained after affective testing in 16/17 subjects). Cold detection thresholds dropped >5°C in all 17 subjects (and were maintained after affective testing in 15/17 subjects). At that timepoint, warmth detection thresholds remained within 1°C of baseline for 12 subjects, within 2°C for 4 subjects, and within 3°C for 1 subject (and were maintained at these levels in 15/17 subjects). Participants who met all pre-established criteria for nerve fiber separation and maintained the criteria after affective testing were labelled "full responders" ($N = 8$) to the A-fiber nerve block; participants whose warmth perception rose more than 1°C or who did not maintain all criteria after affective testing were labelled "partial responders" ($N = 9$).

At the time of maximal nerve fiber separation, the intensity and pleasantness of brushing were again nearly eliminated (**Figure 3**), with significant reductions on the blocked arm relative to the control arm in both pleasantness (blocked arm PRE $M = 31.1$, $SD = 34.0$, POST $M = 5.8$, $SD = 23.3$; control arm PRE $M = 33.8$, $SD = 3.3$, POST $M = 31.1$, $SD = 36.1$, linear mixed effects model, $F(1, 16) = 8.5$, $p = 0.01$, Cohen's $d = 1.35$; Table 1 line e) and intensity (blocked arm PRE *M* = 33.1, *SD* = 25.0, POST *M* = 5.3, *SD* = 9.3; control arm PRE *M* = 34.5, *SD* = 24.5, POST *M* = 32.8, *SD* = 23.8, *F*(1, 16) = 22.2, *p* = <0.001, Cohen's *d* = 1.92; Table 1 line f). Similarly, the intensity and pleasantness of deep pressure were also again nearly eliminated (see **Figure 4**), with significant reductions on the blocked arm relative to the control arm in both pleasantness (blocked arm PRE *M* = 31.0, *SD* = 33.2, POST *M* = 0.5, *SD* = 25.1; control arm PRE *M* = 28.8, *SD* = 33.1, POST *M* = 25.5, *SD* = 36.8, *F*(1, 15) = 10.6, *p* = 0.005, Cohen's *d* = 1.33; Table 1 line g) and intensity (blocked arm PRE *M* = 37.4, *SD* = 23.6, POST *M* = 10.0, *SD* = 12.9; control arm PRE *M* = 37.1, *SD* = 24.2, POST *M* = 31.8, *SD* = 22.6, *F*(1, 15) = 17.8, *p* = <0.001, Cohen's *d* = 1.92; Table 1 line h).

Figure 3 here

Figure 4 here

Across the two studies, changes in pleasantness ratings of brushing and pressure on the blocked arm were correlated, *r* = 0.7, *N* = 22, *p* < 0.001. Changes in intensity ratings of brushing and pressure were similarly correlated, *r* = 0.76, *N* = 22, *p* < 0.001; Table 1 line i. Across the two studies, changes in pleasantness and intensity were not significantly correlated for either brushing (*r* = -0.15, *N* = 22, *p* =0.51) or pressure (*r* = 0.30, *N* = 22, *p* = 0.17). However, on average, a similar magnitude of decrease was observed in pleasantness and intensity for both types of sensation (brushing intensity, *M* = -26.3, brushing pleasantness, *M* = -28.7, pressure intensity, *M* = -29.8, pressure pleasantness, *M* = -27.7).

Table 1. Statistical Table

	Data structure	Type of test	Power / Effect size
a	Non-normal	Linear mixed effects model	Cohen's *d* = 0.55
b	Non-normal	Linear mixed effects model	Cohen's *d* = 0.91
c	Non-normal	Linear mixed effects model	Cohen's *d* = 1.6
d	Non-normal	Linear mixed effects model	Cohen's *d* = 1.7
e	Non-normal	Linear mixed effects model	Cohen's *d* = 1.35
f	Non-normal	Linear mixed effects model	Cohen's *d* = 1.92
g	Non-normal	Linear mixed effects model	Cohen's *d* = 1.33
h	Non-normal	Linear mixed effects model	Cohen's *d* = 1.92
i	Non-normal	Pearson's correlation	

Discussion

The Social Touch Hypothesis (Vallbo, Olausson et al. 1999, Morrison, Loken et al. 2010) proposes the dependence of the pleasantness of gentle skin stroking on C-tactile (CT) afferents, with additional contributions from afferent A-fibers and central processes (e.g. (AB Vallbo 2009)). Recent findings, however, have suggested that afferent A-fibers alone might be sufficient in some cases to generate touch pleasantness(Marshall, Sharma et al. 2019). In the present study, we conducted two type of nerve blocks in healthy adults to selectively reduce A- but not C-fiber function, in an attempt to determine the contribution of A-fibers to touch pleasantness of CT-targeted gentle brushing, as well as deep pressure. Our findings demonstrate that after loss of A-fiber sensation, the perceived intensity *and* pleasantness of gentle brushing and deep pressure are nearly abolished, and these ratings changes are highly correlated. In contrast, these perceptions are maintained in the control arm. These novel findings strongly suggest that afferent A-fiber input- presumably A-beta mechanoreceptive A-fiber- is necessary in the moment of touch for explicit ratings of touch pleasantness, in healthy adults.

In Study 1, a near complete loss of both intensity and pleasantness of gentle brushing and deep pressure was observed after ischemic nerve blockade. This method of nerve block is highly efficient at separating A- and C-fiber function, and blocks somatosensory innervation of the full lower arm. However, it causes a significant amount of discomfort and pain, leaving questions about the effect of this pain on ratings of touch pleasantness. To address this limitation, Study 2 conducted a very similar design using a nerve compression block. This block takes longer to take effect (~1 hour) and affects a much smaller region of skin (dorsal hand near thumb and forefinger)- but does so with minimal discomfort or pain. Study 2 obtained a nearly identical result: near complete loss of both intensity and pleasantness of gentle brushing and deep pressure after the nerve block. In both studies, touch pleasantness and intensity were maintained on the control arm, suggesting that results cannot be attributed to effects of the nerve block procedure on mood, or distracting effects of pain and discomfort. These techniques provide convergent evidence for the dependence of explicit touch pleasantness ratings on afferent A-fibers.

The importance of mechanoreceptive A-fibers to touch pleasantness is consistent with a growing recognition of the complexity of afferent processes in the spinal cord(Abraira, Kuehn et al. 2017, Marshall, Sharma et al. 2019) and brain(Eriksson Hagberg 2019, Hagberg, Ackerley et al. 2019, Schirmer, Lai et al. 2021, Schirmer, Lai et al. 2022), as well as the role of central processes (eg. (McCabe, Rolls et al. 2008, AB Vallbo 2009, Ellingsen, Leknes et al. 2016, Fotopoulou, Von Mohr et al. 2022)), in touch pleasantness. It is also consistent with the pleasantness of touch on the glabrous skin of the hand, although the contribution of its sparse CT innervation is not clear(Loken, Evert et al. 2011, Klöcker, Arnould et al. 2012, Cruciani, Zanini et al. 2021).

Our results are additionally in line with the findings of Marshall and colleagues(Marshall, Sharma et al. 2019, Marshall and McGlone 2020), who reported that ablation of the lamina I-anterolateral pathway at C1/C2 reduced perception of pain, temperature, and itch, but not the pleasantness of slow stroking(Marshall, Sharma et al. 2019). The lamina I-anterolateral pathway is the putative spinal pathway for unmyelinated afferents projecting to the thalamus, as well as the spinohypothalamic and spinoparabrachial pathways. Their result suggests the sufficiency of the dorsal column pathway for explicit perception of touch pleasantness. This could be due to CT fibers joining or modulating the dorsal column pathway below the level of ablation- Marshall and colleagues' 'alternate pathway hypothesis' (Marshall and McGlone 2020). Our data confirm a critical role of A-fibers, likely A-beta mechanoreceptive afferents. Our data are less clear regarding Marshall and colleagues' 'alternate percept hypothesis,' in which early social touch experiences condition associations between A- and C-fiber signals, explaining the sufficiency of dorsal column input. We propose a modified 'alternate percept hypothesis' in which C-fibers condition responses to affective touch, but cannot be interpreted in the absence of corresponding A-fiber input.

Our results additionally demonstrate that afferent A-fibers are critical for the interpretation of the pleasantness of deep pressure. This is not surprising, given the aforementioned association of deep pressure sensation with innervation of deeper tissues suggested by multiple animal and human studies (Kellgren 1948, Kaufman, Longhurst et al. 1983, Mense and Meyer 1985, Abrahams 1986, Lewin and McMahon 1991, Graven-Nielsen, Mense et al. 2004), as well as our work demonstrating its non-*Piezo2* mechanism, which differs from light touch sensation(Case, Liljencrantz et al. 2021). However, the potential contributions of CT fibers to deep pressure pleasantness are unknown.

Our findings are limited by the fact that it is not possible to fully separate A- and C-fiber function by means of nerve block. To mitigate this challenge, we have performed two methods of nerve block whose strengths and limitations complement one another. Through this approach we provide strong convergent evidence for the reliance of gentle stroking pleasantness on A-fiber afferents. An additional limitation to our data is that participants cannot be fully blinded to the nerve block procedure; sensory changes are self-evident. However, participants were naïve to the timeline of anticipated sensory effects and were told that effects of the nerve block on many forms touch are unknown. While we demonstrate that explicit touch pleasantness ratings are highly impacted by A-fiber nerve block, it remains to be tested whether implicit measures of affective response are similarly impacted, confirming the dependence of the full range of CT affective effects on the contribution of afferent A-fibers. For example, CT-targeted touch preferentially activates the zygomaticus ‘smiling’ muscle (Pawling, Trotter et al. 2017)and increases heart rate variability (Triscoli, Croy et al. 2017). Finally, follow-up work is needed to test the mechanisms for a greater variety of affective touch stimuli, including pressure of varying levels, frequencies, and locations.

In sum, our data from two nerve block techniques performed to block afferent A-fiber input in healthy adults confirms that in healthy adults, at the moment of touch, both A- and C-fiber afferents are important contributors to the pleasantness of CT-targeted gentle stroking and deep pressure. This study expands our understanding of the somatosensory pathways that underlie the affective and social effects of touch, and may inform future targets for noninvasive modulation of affect.

References

AB Vallbo, H. O., J Wessberg (2009). Pleasant Touch. Encyclopedia of Neuroscience. L. Squire. Amsterdam, Elsevier.

Abrahams, V. (1986). "Group III and IV receptors of skeletal muscle." Canadian journal of physiology and pharmacology **64**(4): 509-514.

Abraira, V. E., E. D. Kuehn, A. M. Chirila, M. W. Springel, A. A. Toliver, A. L. Zimmerman, L. L. Orefice, K. A. Boyle, L. Bai and B. J. Song (2017). "The cellular and synaptic architecture of the mechanosensory dorsal horn." Cell **168**(1-2): 295-310. e219.

Ackerley, R. (2022). "C-tactile (CT) afferents: evidence of their function from microneurography studies in humans." Current Opinion in Behavioral Sciences **43**: 95-100.

Burgess, P. R. and E. Perl (1967). "Myelinated afferent fibres responding specifically to noxious stimulation of the skin." The Journal of physiology **190**(3): 541-562.

Case, L. K., J. Liljencrantz, N. Madian, A. Necaise, J. Tubbs, M. McCall, M. L. Bradson, M. Szczot, M. H. Pitcher and N. Ghitani (2021). "Innocuous pressure sensation requires A-type afferents but not functional PIEZO2 channels in humans." Nature communications **12**(1): 1-10.

Case, L. K., J. Liljencrantz, M. V. McCall, M. Bradson, A. Necaise, J. Tubbs, H. Olausson, B. Wang and M. C. Bushnell (2020). "Pleasant Deep Pressure: Expanding the Social Touch Hypothesis." Neuroscience.

Chesler, A. T., M. Szczot, D. Bharucha-Goebel, M. Čeko, S. Donkervoort, C. Laubacher, L. H. Hayes, K. Alter, C. Zampieri and C. Stanley (2016). "The role of PIEZO2 in human mechanosensation." N Engl J Med **2016**(375): 1355-1364.

Croy, I., M. T. Fairhurst and F. McGlone (2022). "The role of C-tactile nerve fibers in human social development." Current Opinion in Behavioral Sciences **43**: 20-26.

Cruciani, G., L. Zanini, V. Russo, E. Boccardi and G. F. Spitoni (2021). "Pleasantness ratings in response to affective touch across hairy and glabrous skin: a meta-analysis." Neuroscience & Biobehavioral Reviews **131**: 88-95.

Ellingsen, D.-M., S. Leknes, G. Løseth, J. Wessberg and H. Olausson (2016). "The neurobiology shaping affective touch: expectation, motivation, and meaning in the multisensory context." Frontiers in psychology **6**: 1986.

Eriksson Hagberg, E. (2019). "Investigations of human cortical processing of gentle touch. A study with time-resolved electro-magnetic signal analysis."

Forstenpointner, J., A. Binder, R. Maag, O. Granert, P. Hüllemann, M. Peller, G. Wasner, S. Wolff, O. Jansen and H. R. Siebner (2019). "Neuroimaging Of Cold Allodynia Reveals A Central Disinhibition Mechanism Of Pain." Journal of pain research **12**: 3055.

Fotopoulou, A., M. Von Mohr and C. Krahé (2022). "Affective regulation through touch: homeostatic and allostatic mechanisms." Current Opinion in Behavioral Sciences **43**: 80-87.

Gordon, I., A. C. Voos, R. H. Bennett, D. Z. Bolling, K. A. Pelphrey and M. D. Kaiser (2013). "Brain mechanisms for processing affective touch." Human Brain Mapping **34**(4): 914-922.

Graven-Nielsen, T., S. Mense and L. Arendt-Nielsen (2004). "Painful and non-painful pressure sensations from human skeletal muscle." Experimental brain research **159**(3): 273-283.

Hagberg, E. E., R. Ackerley, D. Lundqvist, J. Schneiderman, V. Jousmäki and J. Wessberg (2019). "Spatio-temporal profile of brain activity during gentle touch investigated with magnetoencephalography." NeuroImage **201**: 116024.

Kaufman, M. P., J. C. Longhurst, K. J. Rybicki, J. H. Wallach and J. H. Mitchell (1983). "Effects of static muscular contraction on impulse activity of groups III and IV afferents in cats." Journal of Applied Physiology **55**(1): 105-112.

Kellgren, J. M., AJ (1948). "On the Behaviour of Deep and Cutaneous Sensibility During Nerve Blocks." Clinical Science **7**(1): 1-11.

Keplinger, M., P. Marhofer, B. Moriggl, M. Zeitlinger, S. Muehleder-Matterey and D. Marhofer (2018). "Cutaneous innervation of the hand: clinical testing in volunteers shows high intra-and inter-individual variability." British Journal of Anaesthesia **120**(4): 836-845.

Klöcker, A., C. Arnould, M. Penta and J.-L. Thonnard (2012). "Rasch-built measure of pleasant touch through active fingertip exploration." Frontiers in Neurorobotics **6**: 5.

Laursen, R. J., T. Graven-Nielsen, T. S. Jensen and L. Arendt-Nielsen (1999). "The effect of differential and complete nerve block on experimental muscle pain in humans." Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine **22**(11): 1564-1570.

Lewin, G. R. and S. B. McMahon (1991). "Physiological properties of primary sensory neurons appropriately and inappropriately innervating skeletal muscle in adult rats." Journal of neurophysiology **66**(4): 1218-1231.

Liljencrantz, J., I. Strigo, D. M. Ellingsen, H. Krämer, L. C. Lundblad, S. S. Nagi, S. Leknes and H. Olausson (2017). "Slow brushing reduces heat pain in humans." European Journal of Pain **21**(7): 1173-1185.

Loken, L. S., M. Evert and J. Wessberg (2011). "Pleasantness of touch in human glabrous and hairy skin: order effects on affective ratings." Brain Res **1417**: 9-15.

Löken, L. S., J. Wessberg, F. McGlone and H. Olausson (2009). "Coding of pleasant touch by unmyelinated afferents in humans." Nature neuroscience **12**(5): 547-548.

Mackenzie, R. A., D. Burke, N. F. Skuse and A. K. Lethlean (1975). "Fibre function and perception during cutaneous nerve block." Journal of Neurology, Neurosurgery & Psychiatry **38**(9): 865-873.

Marshall, A. G. and F. P. McGlone (2020). "Affective touch: the enigmatic spinal pathway of the C-tactile afferent." Neuroscience insights **15**: 2633105520925072.

Marshall, A. G., M. L. Sharma, K. Marley, H. Olausson and F. P. McGlone (2019). "Spinal signalling of C-fiber mediated pleasant touch in humans." Elife **8**: e51642.

McCabe, C., E. T. Rolls, A. Bilderbeck and F. McGlone (2008). "Cognitive influences on the affective representation of touch and the sight of touch in the human brain." Social Cognitive and Affective Neuroscience **3**(2): 97-108.

McGlone, F., A. B. Vallbo, H. Olausson, L. Loken and J. Wessberg (2007). "Discriminative touch and emotional touch." Can J Exp Psychol **61**(3): 173-183.

Mense, S. and H. Meyer (1985). "Different types of slowly conducting afferent units in cat skeletal muscle and tendon." The Journal of Physiology **363**(1): 403-417.

Morrison, I., L. S. Löken, J. Minde, J. Wessberg, I. Perini, I. Nennesmo and H. Olausson (2011). "Reduced C-afferent fibre density affects perceived pleasantness and empathy for touch." Brain **134**(4): 1116-1126.

Morrison, I., L. S. Loken and H. Olausson (2010). "The skin as a social organ." Exp Brain Res **204**(3): 305-314.

Nahra, H. and L. Plaghki (2003). "The effects of A-fiber pressure block on perception and neurophysiological correlates of brief non-painful and painful CO2 laser stimuli in humans." European Journal of Pain **7**(2): 189-199.

Olausson, H., J. Cole, K. Rylander, F. McGlone, Y. Lamarre, B. G. Wallin, H. Krämer, J. Wessberg, M. Elam and M. C. Bushnell (2008). "Functional role of unmyelinated tactile afferents in human hairy skin: sympathetic response and perceptual localization." Experimental Brain Research **184**(1): 135-140.

Olausson, H., Y. Lamarre, H. Backlund, C. Morin, B. Wallin, G. Starck, S. Ekholm, I. Strigo, K. Worsley and Å. Vallbo (2002). "Unmyelinated tactile afferents signal touch and project to insular cortex." Nature neuroscience **5**(9): 900-904.

Pawling, R., P. D. Trotter, F. P. McGlone and S. C. Walker (2017). "A positive touch: C-tactile afferent targeted skin stimulation carries an appetitive motivational value." Biological Psychology **129**: 186-194.

Sailer, U. and S. Leknes (2022). "Meaning makes touch affective." Current Opinion in Behavioral Sciences **44**: 101099.

Schirmer, A., O. Lai, F. McGlone, C. Cham and D. Lau (2021). "Discriminative and affective touch converge: Somatosensory cortex represents Aß input in a CT-like manner." bioRxiv.

Schirmer, A., O. Lai, F. McGlone, C. Cham and D. Lau (2022). "Gentle stroking elicits somatosensory ERP that differentiates between hairy and glabrous skin." Social Cognitive and Affective Neuroscience **17**(9): 864-875.

Torebjörk, H. and R. Hallin (1973). "Perceptual changes accompanying controlled preferential blocking of A and C fibre responses in intact human skin nerves." Experimental brain research **16**(3): 321-332.

Triscoli, C., I. Croy, S. Steudte-Schmiedgen, H. Olausson and U. Sailer (2017). "Heart rate variability is enhanced by long-lasting pleasant touch at CT-optimized velocity." Biological psychology **128**: 71-81.

Vallbo, Å., H. Olausson and J. Wessberg (1999). "Unmyelinated afferents constitute a second system coding tactile stimuli of the human hairy skin." Journal of Neurophysiology **81**(6): 2753-2763.

Wahren, L. K., E. Torebjörk and E. Jörum (1989). "Central suppression of cold-induced C fibre pain by myelinated fibre input." Pain **38**(3): 313-319.

Wasner, G., J. Schattschneider, A. Binder and R. Baron (2004). "Topical menthol—a human model for cold pain by activation and sensitization of C nociceptors." Brain **127**(5): 1159-1171.

Watkins, R. H., M. Dione, R. Ackerley, H. Backlund Wasling, J. Wessberg and L. S. Löken (2021). "Evidence for sparse C-tactile afferent innervation of glabrous human hand skin." Journal of Neurophysiology **125**(1): 232-237.

Ziegler, E., W. Magerl, R. Meyer and R.-D. Treede (1999). "Secondary hyperalgesia to punctate mechanical stimuli." Brain **122**(12): 2245-2257.

Figure Legends

Figure 1. Somatosensory stimuli administered during ischemic compression nerve block. A. Gentle brushing was administered with at a rate of 3 cm/s using a soft goat hair watercolor brush. B. Deep pressure was administered using a commercially available hand massager. C. Vibration sensation was tested using a custom vibration device at 200Hz. D. Perception of warmth was tested using a Medoc thermode.

Figure 2. Somatosensory stimuli administered during nerve compression block. A. Gentle brushing was administered with at a rate of 3 cm/s using a soft goat hair watercolor brush. B. Deep pressure was administered using a commercially available hand massager. C. Vibration sensation was tested using a custom vibration device at 200Hz. D. Perception of cold and warmth were tested using a QST.Lab T09 thermode.

Blocked Arm Intensity Blocked Arm Pleasantness Control Arm Intensity Control Arm Pleasantness

Figure 3. Effect of afferent A-fiber block on intensity and pleasantness of gentle brushing. The intensity and pleasantness of slow gentle brushing on the hand or arm was rated after ischemic or compression nerve block, upon sufficient loss of A-fiber associated sensation. Participants who met all pre-established criteria for nerve fiber separation and maintained the criteria after affective testing are labelled “full responders”; participants whose warmth perception rose more than 1°C or who did not maintain all criteria directly after the brushing task are labelled “partial responders”. For pleasantness ratings, negative numbers indicate unpleasantness.

Blocked Arm Intensity Blocked Arm Pleasantness Control Arm Intensity Control Arm Pleasantness

Figure 4. Effect of afferent A-fiber block on intensity and pleasantness of deep pressure. The intensity and pleasantness of deep pressure was rated after ischemic or compression nerve block, upon sufficient loss of A-fiber associated sensation. Participants who met all pre-established criteria for nerve fiber separation and maintained the criteria after affective testing are labelled “full responders”; participants whose warmth perception rose more than 1°C or who did not maintain all criteria directly after the brushing task are labelled “partial responders”. For pleasantness ratings, negative numbers indicate unpleasantness.