Reduced C-afferent fibre density affects perceived pleasantness and empathy for touch

India Morrison,1,2 Line S. Løken,3 Jan Minde,4 Johan Wessberg,2 Irene Perini,2 Inger Nennesmo5 and Håkan Olausson1,2

Department of Clinical Neurophysiology, Blå stråket 7, Sahlgrenska University Hospital, S-413 45, Gothenburg, Sweden
1 Institute of Neuroscience and Physiology, University of Gothenburg, S-413 90, Gothenburg, Sweden
2 Oxford Centre for functional MRI of the Brain (FMRIB), University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK
3 Department of Surgery, Unit of Orthopedics, Perioperative Sciences, Umeå University Hospital, S-901 85, Umeå, Sweden
4 Department of Pathology, Karolinska University Hospital, Huddinge, S-141 86, Stockholm, Sweden
5 Correspondence to: India Morrison, Department of Clinical Neurophysiology, Blå stråket 7, Sahlgrenska University Hospital, S-413 45 Gothenburg, Sweden
E-mail: india.morrison@neuro.gu.se

We examined patients with a heritable disorder associated with a mutation affecting the nerve growth factor beta gene. Their condition has been classified as hereditary sensory and autonomic neuropathy type V. Carriers of the mutation show a reduction in density of thin and unmyelinated nerve fibres, including C afferents. A distinct type of unmyelinated, low-threshold mechanoreceptive C fibre, the C-tactile afferent, is present in hairy but not glabrous skin of humans and other mammals. They have been implicated in the coding of pleasant, hedonic touch of the kind that occurs in affiliative social interactions. We addressed the relationship between C fibre function and pleasant touch perception in 10 individuals from a unique population of mutation carriers in Sweden. We also investigated the effect of reduced C-fibre density on patients’ evaluation of observed interpersonal touch (empathy). Results showed that patients perceived gentle, slow arm stroking, optimal for eliciting C-tactile afferent responses (1–10 cm/s), as less pleasant than did matched controls and also differed in their rating patterns across stimulation velocities. Further, patients’ blood-oxygen-level-dependent responses in posterior insular cortex—a target for C afferents—were not modulated by stimulation optimal for activating C-tactile afferents. Hence, perception of the hedonic aspect of dynamic touch likely depends on C-tactile afferent density. Closely similar patterns between individuals’ ratings of felt and seen touch suggest that appraisal of others’ touch is anchored in one’s own perceptual experience, whether typical or atypical.

Keywords: tactile C afferent; HSAN-V; pleasant touch; nerve growth factor beta gene; empathy
Abbreviations: HSAN = hereditary sensory and autonomic neuropathy; NGFB = nerve growth factor beta

Introduction

The sense of touch is essential for determining the location of a stimulus on the skin surface, for haptic exploration and for object manipulation. However, these well-established discriminative aspects of touch are complemented by an affective aspect that has only recently begun to be scientifically investigated (McGlone et al., 2007). This affective dimension of touch involves
inter-individual contact, affiliative behaviour and the formation and maintenance of relationships (Morrison et al., 2010; Olausson et al., 2010). Such affective aspects may form a functional category of touch distinct from the more well-known discriminative functions.

Evidence that distinct neural pathways play a role in affect-related touch information comes from research both on the peripheral and central levels. On the peripheral level, a type of unmyelinated C fibre, the tactile C afferent, has been shown to be very sensitive to innocuous tactile stimulation (Nordin, 1990; Vallbo et al., 1999; Wessberg et al., 2003). Tactile C afferents are slow-conducting, easily fatigued and often show after-discharge, i.e. they may continue to fire for several seconds after stimulus withdrawal (Vallbo et al., 1999). Although these properties render them suboptimal for sensory discrimination, they show many characteristics consistent with a role in selectively encoding affective touch information. Most notably, they preferentially respond to stroking over the skin surface within a velocity range (1–10 cm/s) that is also rated as most hedonically pleasant, as opposed to slower or faster speeds (Löken et al., 2009). Tactile C afferents are found only in hairy skin and are absent in the glabrous (smooth) skin of the palms (Olausson et al., 2010).

On the central level, tactile C-afferent pathways project to the insular cortex (Olausson et al., 2002, 2008a). Stimulation of tactile C fibres on the arm and thigh also produce somatotopically organized activations in posterior insular cortex (Björnsdotter et al., 2009). The response in posterior insular cortex shows a similar velocity selectivity as tactile C fibres (Morrison et al., 2008). This cortical region plays an important role in representing information relevant to well-being (Craig, 2003, 2009).

The type of slow, gentle stimulation of hairy skin that activates tactile C receptors is likely to occur during social interactions (Morrison et al., 2010). Another aspect of social touch involves the recognition of pleasant, affective touch interactions in others. For the social brain, others’ actions and situations supply a rich source of information about objects, contexts and even mental and emotional states. Recent research suggests that brain areas involved in directly experienced touch (Keysers et al., 2004; Blakemore et al., 2005; Ebisch et al., 2008; Morrison et al., 2008; Schaefer et al., 2009) and pain (Morrison et al., 2004, 2007a; Singer et al., 2004; Jackson et al., 2006; Morrison and Downing, 2007) can be activated by seeing others undergoing tactile or painful stimulation (empathy). Such responses to observed touch and pain may underlie recognition of others’ sensory states and provide ‘free’ information about objects or situations (Danziger et al., 2006; Morrison et al., 2007b; Morrison and Downing, 2007).

In order to test the relationship between tactile C-fibre function and directly experienced as well as observed touch, we investigated aspects of gentle tactile stimulation in a unique group of cognitively normal patients with a reduced number of C-afferent fibres. Their condition has been classified as hereditary sensory and autonomic neuropathy type V (HSAN-V) and involves reduced pain and temperature sensitivity (Einarsdottir et al., 2004; Minde et al., 2004). HSAN is a group of rare hereditary neuropathies with sensory (and to a varying degree autonomic) deficits that has been further classified into five different types, depending on mode of inheritance, neuropathology and clinical symptoms (Dyck et al., 1983). Gene loci have been identified for most of the HSAN subtypes. Our patients with HSAN-V are associated with a mutation affecting a gene involved with nerve growth factor beta (NGFB; Online Mendelian Inheritance in Man 608654) (Einarsdottir et al., 2004).

The mutation (R221W, an arginine to tryptophan change on amino acid 100 in the mature protein) is located on the β-subunit of the NGF gene (NGFB) (Einarsdottir et al., 2004). It has been traced by pedigree to a common ancestor in the 17th century (Minde et al., 2006). The mutation results not in a complete loss of NGF function but a reduced availability of active protein, likely hampering development of sensory fibres (Larsson et al., 2009). Carriers exhibit severe to moderate reduction of unmyelinated C fibres and a moderate reduction of thinly myelinated Aδ fibres in sural nerve and skin biopsies (Minde et al., 2006, 2009; Axelsson et al., 2009). The patients have no reduction of large diameter myelinated (Aβ) fibres (Minde et al., 2006, 2009).

The group of patients exhibiting the HSAN-V mutation is a population of consanguineous individuals geographically dispersed in the Norrbotten region in the north of Sweden, along the Torne River Valley. The HSAN-V haplotype common to all carriers is located on chromosome 1 (1p11.2-13.2) and is flanked by single nucleotide polymorphism markers rs2490334 and rs2275607 (Einarsdottir et al., 2004). Carriers present with varying degrees of pain insensitivity, particularly deep pain insensitivity, associated with joint deformation and painless bone fractures. Homozygous individuals are severely affected (with joint deformations and disturbances in deep pain sensation), whereas heterozygous carriers present with symptoms to varying degrees, in some cases showing a progression of the disease. They have normal cognitive functions (Minde et al., 2006, 2009). Unlike in other HSAN disorders, autonomic dysfunction is not a prominent trait, although several individuals display pathological orthostatic tests and diminished sympathetic skin responses (Einarsdottir et al., 2004; Minde et al., 2004, 2006, 2009).

Here, we tested the hypothesis that tactile C fibres play a central role in pleasant touch perception by assessing subjective responses to skin stroking at five different velocities (0.3–30 cm/s) in the thin fibre denervated patient group. Since thinly myelinated Aδ fibres do not signal light touch in humans (Olausson et al., 2002, 2008b), any differences in tactile perception would be related to tactile C-afferent function. We predicted that the patients’ reduction in thin C-afferent density would be associated with a reduction in perceived pleasantness of dynamic touch but not in discriminative touch capacity. Further, we tested whether any such altered perception of touch pleasantness would influence the evaluation of touch pleasantness in others during touch observation (touch empathy). We predicted that the individual rating patterns for visually observed touch would closely match those for directly experienced touch, indicating that evaluation of others’ touch interactions draws on information from affect-related tactile pathways.
Materials and methods

Participants

Patients and controls gave informed consent approved by the University of Gothenburg ethics committee and in accordance with the Declaration of Helsinki, and received financial compensation for their participation.

Ten individuals (age 17–73 years, mean age 45; five female) sharing a missense mutation of the NGFB gene, resulting in HSAN type V, were included in the study (Supplementary Table 1). Three (Cases 1–3, Supplementary Table 1) were homozygous (having the mutation on both alleles) and the rest heterozygous (having the mutation on one allele). The patients have, to different degrees, reduced temperature and pain sensations, notably deep pain insensitivity (Minde et al., 2004, 2006, 2009). The most affected suffer from painless fractures, bone necrosis, osteochondritis and joint destruction leading to severe Charcot arthropathy (Einarsdottir et al., 2004; Minde et al., 2004, 2006, 2009). One patient (Case 2) suffers from orthostatic hypoten-

dion and in two patients (Cases 2 and 3) sympathetic skin responses could not be recorded. They all have normal cognitive functions and consider themselves to have normal touch sensibility with no history of alldynia or hyperalgasia. All patients for whom data are available (7/10) show a moderate to severe reduction in Aδ and C fibres in nerve and skin biopsies. They have normal motor and sensory neuro-

graphy (except for median nerve compression at the level of the carpal tunnel in Cases 5, 6 and 8) indicating intact function of Aδ fibres, and no other neurological disease besides the HSAN-V neuropathy (Supplementary Table 1). They did not take any drugs that influence neurological function.

The patients’ shared NGFB mutation was maintained in the popula-
tion through consanguineous marriages (e.g. among cousins) over sev-
eral generations following the lifetime of the common ancestor in the 17th century. The population is now geographically dispersed over the large Norrbotten region north of the Arctic Circle in Sweden. Therefore the carriers do not necessarily know each other and can be separated from one another by several generations.

The disease shows a progressive trend, with mildly or unaffected carriers developing symptoms with increasing age in some cases and worsening symptoms in others (Minde et al., 2004). However, it should be emphasized that all patients with HSAN-V shared the same mutation haplotype on the NGFB gene (Einarsdottir et al., 2004).

Ten neurologically healthy individuals (ages 18–77, mean age 45; five female) participated in the study. Individuals were matched to the patient participants on the basis of age, sex and length of education.

Stimuli and procedures

Discriminative touch

Tactile directional sensibility was tested on the left dorsal forearm using a hand-held stimulator that was moved with a speed of 1 cm/s (Supplementary Fig. 1, for details see online Supplementary Material). A forced-choice method was used and the stimulator was moved over a predetermined distance in either proximal or distal di-

eriction in a pseudorandom order (Nornell et al., 2001; Løken et al., 2011). The participant was instructed to have his/her eyes closed and verbally report the direction of the movement. The result was sum-

marized in a response profile area (theoretical range 18–90) that pro-

vided a quantitative measure of the directional sensibility of the subject’s forearm (the lower the response profile area value the better the directional sensibility).

Pleasant touch

Stimuli to assess participants’ responses to gentle touch consisted of single brush strokes over 10 cm of left forearm skin using a soft 70 mm wide goat-hair artist’s brush. Brush strokes were delivered manually in a proximal to distal direction at five different velocities: 0.3, 1, 3, 10 and 30 cm/s. All stimulations were performed by I.M. who was trained in the delivery of the stimuli and during the experiment was guided regarding brushing velocity by a visual meter (on a monitor not visible to the subject).

Stimuli were presented in three blocks with two repetitions of each velocity, for a total of six trials/velocity. Participants were seated in front of a laptop monitor showing a visual-analogue scale, with the anchor points ‘unpleasant’ (−10) and ‘pleasant’ (10). In each trial instructions appeared above the visual-analogue scale to ‘rate how pleasant the touch feels to you’ followed by a 4–6 s response interval. Participants were wearing goggles flanked by occluders that ensured that their arm and the experimenter were out of view.

Pleasant touch observation

Short videos depicting strokes on another person’s forearm skin were randomly intermixed with the tactile stimulus trials within the three blocks. The same velocities were used in videos and tactile trials. As with tactile trials, two visual trials were delivered per block, for a total of six trials/velocity. The video clips showed a hand moving over 10 cm of a model’s skin against a neutral black background (Fig. 2B). As with the tactile trials, participants registered their ratings on the visual-analogue scale after each trial, with the instruction ‘rate how pleasant you think the touch feels to the person in the video’. It was made clear to participants that the ‘person in the video’ referred to the recipient of the stroking (the model) rather than the person performing the stroking. The models were either male or female and arms were presented from either an allocentric or egocentric viewpoint (gender and viewpoint were randomized but not considered as factors, as pilot data showed no effect of either variable on ratings).

TACTYPE questionnaire

At the end of the testing session, participants were administered a Swedish translation of the 15-item TACTYPE questionnaire (Deethardt and Hines, 1983). Most questions focused on the affective aspect of interpersonal touch behaviour in social situations, particu-\n
larly in opposite-sex relationships (participants were instructed to an-
swer as they would if they were in such a relationship). An example item is: ‘I enjoy touching my girlfriend/boyfriend when greeting that person’. Participants reported their degree of agreement with each item using a 5-point scale ranging from ‘totally disagree’ to ‘totally agree’.

Statistics

All data were analysed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) and R (R Foundation for Statistical Computing, Vienna, Austria). Data were first analysed by averaging the visual-analogue scale scores given by each participant for each velocity and these average ratings were used in the reported ANOVA and multiple linear regression analyses for single sets of data (that is, patients or controls; visual or tactile modality). This was the same approach used to investigate tactile C discharge and
visual-analogue scale pleasantness rating patterns in Löken et al. (2009). An extensive analysis that allowed for the repeated measures at each velocity was then implemented using mixed random and fixed effects modelling (Littel et al., 2009). This model also allowed direct statistical tests for differences between groups (patients, controls) and modalities (tactile, visual). The models were fitted using Restricted Maximum Likelihood and an unstructured covariance matrix, similar to multiple linear regression. The findings reported in the present study were robust with regard to assumptions about covariance structure and various types of mixed effect models were extensively explored without altering the significance levels of the reported findings. We also fitted the same models using ranks of all visual-analogue scale ratings instead of visual-analogue scale values, hence limiting visual-analogue scale to an ordinal scale. The reported findings and significance levels were the same for visual-analogue scale ranks as for visual-analogue scale scores.

Cortical correlates of tactile C stimulation

The posterior insular cortex is a target for tactile C-afferent projections (Olausson et al., 2002; Björnsdotter et al., 2009). A separate experiment aimed to rule out the possibility that patients’ low density of tactile C afferents is sufficient to activate posterior insula. Blood-oxygen-level-dependent responses to brush stroking on the forearm at a tactile C-optimal stroking velocity (3 cm/s) and at a non-optimal stroking velocity (30 cm/s) were assessed in five patients using functional MRI. We performed a search for voxels showing the greatest signal change for 3 cm/s, the stroking speed most likely to elicit tactile C activation and a pleasant percept in healthy individuals (Löken et al., 2009). Differences in blood-oxygen-level-dependent response between 3 and 30 cm/s stimulation, likely reflecting signalling from tactile C-afferent projections to cortex, were compared in the patient sample (n = 5) and in a sample of healthy volunteers (n = 5). Statistical maps for both patient and healthy participant groups were thresholded at P = 0.0005, with a family-wise-error corrected cluster threshold of 20 voxels (P < 0.05). See online Supplementary Material for details of the stimuli, data acquisition and data analysis.

All participants gave informed consent approved by the University of Gothenburg and Sahlgrenska University Hospital, in accordance with the Declaration of Helsinki. Travel expenses for patients’ travel from the far north of Sweden to Gothenburg were paid. Eight patients (three homozygotes) were recruited for the study but data for two of them were excluded due to excessive motion in one case and insufficient wakefulness in the other. No data were acquired from one patient who became panicked in the scanner. The final patient group consisted of five individuals: one homozygous female, one homozygous male, two heterozygous males and one heterozygous female (mean age 52; see online Supplementary material). The healthy group consisted of five gender-matched volunteers recruited from the University of Gothenburg (three female; mean age 25). Participation was compensated at 200 Swedish crowns (~20 Euro) per session.

Results

Discriminative touch

The directional sensibility test used to measure discriminative touch is very sensitive in detecting dysfunction of myelinated Aβ fibres (Olausson et al., 1997; Norrsell et al., 2001) (Supplementary Fig. 1). C-fibre denervated patients (n = 10, Supplementary Table 1) and age-, sex- and education-matched healthy control subjects (n = 10) performed equally well on the test (Wilcoxon signed ranks test, P = 0.47; patients’ median response profile area = 18, range 18–38; healthy controls’ median response profile area = 18, range 18–25), and all results were well within the earlier established normal range (Olausson et al., 1997; Norrsell et al., 2001).

Evaluation of touch pleasantness

For brush stroking on the forearm, the control group’s ratings were consistent with previously published results from another group of healthy subjects (Löken et al., 2009). The mean pleasantness ratings for each velocity for patients and healthy participants were compared using a two-way ANOVA with factors group (patient, healthy control) and velocity. Post hoc t-tests revealed that patients rated brush stroking as significantly less pleasant compared with controls (F(1, 94) = 14.5, P < 0.001; Fig. 1). Patients’ ratings also had a higher coefficient of variance compared with controls (P < 0.001, independent samples t-test).

To determine the effect of stroking velocity on the pattern of pleasantness ratings between groups, regression analyses specifically assessing the shape of rating curves were performed on the patient and control groups separately. The independent variable ‘velocity’ was logarithm-transformed and entered as linear and quadratic terms in a regression model. A negative quadratic term in the regression captures the unique, inverted U-shaped rating pattern correlated with tactile C-afferent discharge in healthy subjects (Löken et al., 2009). For the control group, the negative quadratic term provided a significantly better fit than a linear term (P < 0.001), as in earlier research (Löken et al., 2009). In contrast, for the patient group the negative quadratic term did not supply a significantly better fit than a linear term (P = 0.13; test for comparison of regression models) (Chatterjee and Hadi, 2006).

As a direct test between the shapes of the regression (reflecting rating patterns across velocities) for patients and controls, we performed an extended mixed random- and fixed-effects model for repeated measures in which all the visual-analogue scale ratings from the two groups were taken into account (Littel et al., 2009). This involves performing a standard significance test of the quadratic term, then performing a statistical comparison between groups using a model implemented in SPSS. Statistical analysis of this model showed that the quadratic regression term for velocity was significantly negative for healthy controls but non-significant for patients (P = 0.022 for the difference in quadratic term). The visual-analogue scale intercept was also significantly lower for patients compared with controls (P = 0.019). We found no other statistical differences in visual-analogue scale ratings between patients and controls.
Evaluation of touch pleasantness in others

Just as for the tactile ratings, each individual’s mean pleasantness rating of the video stimuli for each velocity for both patient and control groups were compared using a two-way ANOVA with factors group (patient, control) and velocity. Post hoc t-tests revealed that patients rated observed brush stroking as significantly less pleasant compared with controls \[F(1, 94) = 23.2, P \leq 0.001; \text{Fig. 2}\]. Patients’ ratings also had a higher coefficient of variance compared with controls \((P \leq 0.001, \text{independent samples} \text{ t-test})\).

To determine the effect of stroking velocity on the pattern of pleasantness ratings between groups, regression analyses specifically assessing the shape of rating curves were performed on the patient and control groups separately. Like the tactile regression analysis, a model with a quadratic term supplied the best fit for controls \((P < 0.001)\), but did not provide a significantly better fit compared with a linear model for patients \((P = 0.54)\). The lack of improved fit for a quadratic model in the patients indicated that they differed significantly from controls’ psychophysical rating patterns across velocities when assessing touch in others.

As for tactile visual-analogue scale ratings, we performed an extended mixed model regression analysis where all the ratings were taken into account, allowing for direct tests between the regression parameters in the two groups. The visual-analogue scale intercept was significantly lower in patients compared with controls \((P = 0.0022)\), and the quadratic regression term for velocity was non-significant for patients but significantly negative for healthy controls \((P = 0.0049 \text{ for the difference})\). There were no other statistical differences in visual-analogue scale ratings between patients and controls.
Relationship between felt and seen touch

To investigate the relationship between estimation of felt and visually observed tactile stimulation, mean ratings for patients and controls were submitted to a two-way ANOVA with the factors group (patient, control) and modality (tactile, visual). There was no interaction between group and modality \( F(1, 194) = 0.003, P = 0.95 \). There was a main effect of group \( F(1, 194) = 42.1, P < 0.001 \), but no effect of modality \( F(1, 194) = 1.6, P = 0.21 \). The main effect of group indicated differences in rating patterns between patients and controls regardless of modality. The lack of an effect of modality on ratings further confirmed that within groups, pleasantness rating patterns were similar across velocities, regardless of touch being felt or merely seen (Fig. 3).

This analysis was also done using an extended mixed model regression analysis where all the visual-analogue scale ratings for both groups (patients, controls) and both modalities (tactile, visual) were taken into account. As described earlier, visual-analogue scale ratings were statistically lower in patients \( P = 0.0035 \) and the quadratic regression term was significantly different \( P = 0.00073 \) and negative in controls.

TACTYPE questionnaire

There was no significant difference in mean score between the patient (mean score = 49.7) and control groups (mean score = 55.7, \( P = 0.33 \), t-test). Out of 10 patients, one fell in
Category 1 (high tactile receptivity/expressiveness), five in Category 2, two in Category 3 and two in Category 4 (low tactile receptivity/expressiveness). Out of 10 controls, two fell in Category 1, three in Category 2, four in Category 3 and one in Category 4. These results suggest that the patients did not differ from controls in self-report of how they perceive and use touch in social relations.

Blood-oxygen-level-dependent responses in posterior insular cortex

As predicted, the posterior insular cortex in the healthy participants showed the greatest blood-oxygen-level-dependent signal increase for 3 cm/s stroking on the forearm ($x, y, z = 31, -20, 11$; Fig. 4). However, this tactile C-optimal stimulation failed to capture insular activation in the patients (Fig. 4). To explore the posterior insular response further, a region of interest mask created from the healthy group’s activation cluster was applied to the patient group’s data. Mean parameter estimates ($β$-values) were extracted for each voxel time course. The healthy group showed a significant difference between 3 and 30 cm/s stimulation ($P = 0.01$), likely reflecting functionally specific tactile C-afferent input to posterior insula. In contrast, for the patient group there was no difference between the two velocities, likely reflecting reduced tactile C input to cortex. Statistical maps for both patient and healthy participant groups were thresholded at $P = 0.0005$, with a family-wise-error corrected cluster threshold of $≥20$ voxels ($P < 0.05$).

**Discussion**

In this study, we investigated the underpinnings of pleasant touch in the peripheral nervous system, and their effects on the evaluation of observed touch, by examining a unique group of patients.
Pleasant touch

Certain varieties of tactile experience are accompanied by an affective or positively hedonic component. Gentle stroking along the skin surface is generally considered pleasant. It tends to occur in specific social contexts (Morrison et al., 2010), though its prevalence in the population or across cultures has never been empirically assessed. Recent microneurography research (recordings from single afferent nerve fibres of awake volunteers) has established the importance of brush stroking speed on both tactile C-afferent discharge and subjective pleasantness ratings. Intermediate velocities (1–10 cm/s) activate unmyelinated tactile C receptors more effectively than slower (0.1 and 0.3 cm/s) or faster (30 cm/s) stroking speeds. Intermediate velocities are also perceived as more pleasant than slower or faster velocities (Løken et al., 2009). In contrast, other tactile receptor types (myelinated slowly adapting type I, slowly adapting type II, field and hair receptors) consistently increase firing rate with stroking speed. These findings suggest that among skin afferents, tactile C afferents uniquely encode aspects of gentle stroking that are experienced as pleasant. In this study, pleasantness is considered to reflect conscious, subjective evaluation of the tactile sensation and any positive emotions associated with it (Berridge and Kringelbach, 2008), as measured by subjects' ratings on a visual-analogue scale ranging from ‘unpleasant’ to ‘pleasant’.

Compared with healthy, age- and education-matched controls, C-fibre denervated patients’ mean pleasantness ratings were lower (less pleasant) indicating reduced positive hedonic evaluation of the stimulus. Most crucially, the rating pattern across the five different velocities for C-fibre denervated patients deviated from that of controls. The rating pattern in healthy subjects follows an inverted U-shaped curve, which is highly correlated with tactile C-afferent discharge across velocities (Løken et al., 2009). A quadratic term was used in a regression model to capture this pattern (see also Løken et al., 2009). The control group had a significantly better fit with this quadratic term than the patients, indicating that the patient group’s perceptual evaluation of the stimuli deviates from the typical pattern associated with tactile C firing. The patient group’s rating curve across velocities was also significantly flatter compared with the control group’s. The C-denervated patients’ atypical perception suggests a central role for tactile C afferents in the normal perception of gentle, dynamic touch stimuli.

In contrast to healthy participants, the tactile C-optimal stroking speed of 3 cm/s failed to activate the posterior insula in patients and there was no significant blood-oxygen-level-dependent difference between 3 (tactile C-optimal) and 30 cm/s (tactile C-non-optimal) stroking speeds in patients’ posterior insula (Fig. 4). This is consistent with compromised tactile C-afferent input to this area.

Neuroimaging evidence from patients with selective damage to large-diameter myelinated afferent fibres indicates that tactile stimulation of spared unmyelinated C fibres activates specific regions of the insular cortex (Olausson et al., 2002; Løken et al., 2009), a brain area implicated in the subjective evaluation of the body’s condition (Craig, 2009). Tactile C-fibre inputs to posterior insular regions are also somatotopically organized with respect to tactile receptive fields in the arm and thigh (Björnsdotter et al., 2009).

The cumulative evidence from microneurography and neuroimaging studies has prompted the hypothesis that tactile C fibres carry information destined for affective processing: tactile C-afferent activation is both closely correlated with touch pleasantness (Løken et al., 2009) and sufficient for it in the absence of myelinated tactile afferent input (Olausson et al., 2002). Thus tactile C afferents may represent a first stage for encoding the affective dimension of touch (Björnsdotter et al., 2010; Morrison et al., 2010). It should be emphasized, however, that despite its selectivity for pleasant dynamic touch stimuli, the human tactile C-insula pathway is probably neither necessary nor sufficient for all types of pleasantness perception in the tactile domain. For example, soft velvet feels pleasant on the palm skin (Francis et al., 1999), which lacks tactile C-afferent receptors. In evaluating the pleasantness of gentle stroking stimulation on the arm, it is likely that the patients rely on an Aβ-afferent-somatosensory cortex pathway to a greater extent than do controls. This discriminative pathway can distinguish among stimulus speeds but may be less direct than the tactile C-insula pathway in its integration of velocity information with affective processing. Such compensation may manifest at the level of altered hedonic evaluation without marked adverse effects on self-report of interpersonal touch, as suggested by the failure of a questionnaire about perception and use of touch in social communication to capture differences between patients and controls.

The reduction in C-fibre density in the patients with HSAN-V is likely to disrupt the tactile C-insula pathway through developmental or regulatory effects of the abnormal NGFB expression.
associated with the mutation. In rat cell lines, this mutation is associated with a decrease in availability of mature nerve growth factor protein (Larsson et al., 2009). Such disruption may affect downstream cortical pathways, resulting in altered hedonic evaluation of the stimulus. One possibility is that nerve growth factor levels affect the expression of proteins in peripheral sensory axons; this is supported by evidence of localized hypersensitivity to mechanical stimulation following nerve growth factor injection in humans (Rukwied et al., 2010). The possibility that congenitally reduced nerve growth factor would result in hyposensitivity to mechanical stimuli is thus reasonable.

Here, soft brush stroking was delivered manually, whereas in a previous study we used a robotic tactile stimulator to deliver tactile stimuli with precise control over velocity and force (Løken et al., 2009). Nevertheless, the control subjects’ visual-analogue scale ratings across velocities in the present study were similar to the visual-analogue scale ratings obtained in the previous study \((n = 20)\) and thus probably representative of healthy subjects in general. The close resemblance in the ratings for felt and observed touch for patients as well as controls (discussed in the following section) also indicates that the participants handled the visual-analogue scale in a consistent manner.

It is important to note that a local skin deformation that strongly activates a single given tactile C afferent does not in itself produce a sensation of pleasant touch (Valbo et al., 1999). Therefore the relationship between tactile C discharge/innervation and psychophysics is best approached at the population level. Within the sample of the patient population studied here, no systematic differences were discovered between individual results for homozygous \((n = 3)\) or heterozygous \((n = 7)\) patients. However, individual rating patterns segregate patients and controls significantly, and of the two patient outliers, one is heterozygous and one homozygous (see Supplementary Fig. 2 for a scatterplot). Two of the homozygous individuals were markedly atypical in their rating patterns (Supplementary Material). Further research will explore the population as a whole (to improve understanding of the distribution) and individual case studies (to improve understanding of the mutation’s effects).

**Pleasant touch observation: touch empathy**

Hedonic-affective perception of the gentle stroking stimulation—distinct from discriminative tactile processing—may be of particular relevance in social contexts.

Considering that the velocity of skin stroking is a crucial variable for coding in tactile C pathways, the velocity of an observed touch may provide the observer with a critical cue for recognizing the affective nature of the observed touch interaction. Such cues could ultimately enable potential representations about others’ emotions, motivations, intentions and social relationships. If evaluation of touch pleasantness in others depends on similar mechanisms as those involved in evaluation of directly experienced touch, tactile C pathways may play a role in shaping such responses.

The patients with denervated C fibres demonstrated altered perception of touch pleasantness. Yet since patients with HSAN-V have normal social skills and cognitive functions (de Andrade et al., 2008), they may nevertheless have learned what is generally considered a pleasant stroking speed during their interactions with others. Self-related and other related evaluations may follow different, relatively independent norms, depending on experience and context. An alternative possibility is that the evaluation of how pleasant a touch might be to another person is shaped by direct perceptual experience and draws on the same norms.

To address these alternatives, subjects viewed video clips of others’ arms being stroked and were asked to rate how pleasant they thought the touch might feel to the person being stroked in the video. The control group’s ratings followed the typical inverted-U curve, with a quadratic term providing a significant fit in the regression model. However, like their ratings for directly experienced touch, the patients’ ratings of the videos did not follow this pattern; the quadratic term was not significant.

When the effect of modality (felt or seen) was investigated across control and patient groups, analysis revealed a main effect of the group factor but not of the modality factor. This suggests that subjects rated felt and seen touch similarly across velocities within each group, regardless of the overall differences in rating patterns between groups. These findings support the hypothesis that observed touch is perceived with reference to first hand touch experience.

They are also consistent with extensive findings in social neuroscience that our ability to recognize and process social information may rely on brain mechanisms that relate others’ motor, sensory and emotional experiences to our own. These mechanisms may operate economically by using some of the same neural resources for observation as for experience. For example, it has been demonstrated that seeing a painful mishap happen to someone else engages cortical regions that are also involved in representing the affective-motivational (Singer et al., 2004; Morrison and Downing, 2007; Morrison et al., 2007) and sensory (Avenanti et al., 2005; Bufalari et al., 2007) aspects of our own pain and that ‘empathizing’ with others’ touch recruits cortical sensory areas (Keysers et al., 2004; Blakemore et al., 2005).

Visual processing may thus utilize the local cortical computations that are informed by velocity-based tactile processing in tactile C pathways. An alternative to such a ‘common coding’ mechanism (Prinz, 1990) in this case is cross-modal priming, in which the activation of tactile-related populations by actual touch primes by association the response to the touch videos (or vice versa). However, any complete account of the neural mechanism involved must also explain why altered response profiles in one modality would give rise to such similar profiles in the other. Regardless of the precise nature of the mechanism, these results demonstrate that the experience of felt and seen pleasant touch are linked.

**Conclusion**

These findings suggest a role for tactile C afferents in normal hedonic perception of dynamic touch stimulation and that the evaluation of others’ dynamic touch is based on first hand experience of its hedonic-affective aspects. Reduced tactile C-afferent input to posterior insula, as a result of the NGFB mutation, is likely to be
the main factor driving the differences between patients and controls.

**Acknowledgements**

We thank Å. Vallbo, M.C. Bushnell, R.D. Johnson, U. Norrrell and S. Leknes for kindly reading the article and offering advice. We thank E. Jörn for inclusion of data from HSAN-I patients for Supplementary Materials. We also thank K. Göthner and Tomas Carlsson for technical assistance.

**Funding**

Swedish Research Council (grants 2006-2255 and 2007-2635 to I.M., 62X-3548 to J.W., and 2007-2912 to H.O.); the Sahlgrenska University Hospital, Marianne and Marcus Wallenberg Foundation (MMW 2009.0080 to H.O.); Norrbotten Research Institute (FOU) (grant FOU NLL 2008-2 to J.M.); Kempe Foundation (grant JCK-2832 to J.M.).

**Supplementary material**

Supplementary material is available at Brain online.

**References**


Norrsell U, Eliasson B, Frizell M, Wallin BG, Wesslau C, Olausson H.
Olausson H, Wessberg J, Morrison I, McGlone F, Vallbo Å. The neuro-
Unmyelinated tactile afferents signal touch and project to insular
Unmyelinated tactile afferents have opposite effects on insular
and somatosensory cortical processing. Neurosci Lett 2008a; 436:
128–32.
Functional role of unmyelinated tactile afferents in human hairy skin:
sympathetic response and perceptual localization. Exp Brain Res
Olausson H, Norrsell U, Göthner K, Wallin BG. Directional sensibility for
Perl ER. Myelinated afferent fibres innervating the primate skin and their
Prinz W. A common coding approach to perception and action. In: Neumann O, Prinz W, editors. Relationships between perception and
Rukwied R, Mayer A, Kluuschina O, Obreja O, Schley M, Schmelz M.
NGF induces non-inflammatory localized and lasting mechanical
Schaefer M, Xu B, Flor H, Cohen LG. Effects of different viewing per-
pectives on somatosensory activations during observation of touch.
Singer T, Seymour B, O’Doherty J, Kaube H, Dolan RJ, Frith CD.
Empathy for pain involves the affective but not sensory components
Vallbo ÅB, Olausson H, Valberg J. Unmyelinated afferents constitute a
second system coding tactile stimuli of the human hairy skin.
Vallbo ÅB, Olausson H, Wessberg J, Kakuda N. Receptive field charac-
teristics of tactile units with myelinated afferents in hairy skin of
Wallin BG, Olausson H, Fernström KW, Vallbo ÅB. Receptive field
properties of unmyelinated tactile afferents in the human skin.