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Review

Slow touch and ultrafast pain fibres: Revisiting peripheral nerve classification

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HIGHLIGHTS

- Conduction velocity of peripheral somatosensory afferents has been intimately linked to function.
- Recently, the classical relation between nerve conduction and function has become blurred.
- We review evidence for C fibres signalling touch and Aβ fibres signalling pain with implications for taxonomy.

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ABSTRACT

One hundred years ago, Erlanger and Gasser demonstrated that conduction velocity is correlated with the diameter of a peripheral nerve axon. Later, they also demonstrated that the functional role of the axon is related to its diameter: touch is signalled by large-diameter axons, whereas pain and temperature are signalled by small-diameter axons. Certain discoveries in recent decades prompt a modification of this canonical classification. Here, we review the evidence for unmyelinated (C) fibres signalling touch at a slow conduction velocity and likely contributing to affective aspects of tactile information. We also review the evidence for large-diameter Aβ afferents signalling pain at ultrafast conduction velocity and likely contributing to the rapid nociceptive withdrawal reflex. These discoveries imply that conduction velocity is not as clear-cut an indication of the functional role of the axon as previously thought. We finally suggest that a future taxonomy of the peripheral afferent nervous system might be based on the combination of the axoṅs molecular expression and electrophysiological response properties.

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1. The history of peripheral nerve classification

One hundred years ago, in 1924, Joseph Erlanger and Herbert Gasser, working at the Medical School at Washington University, St. Louis, MO, U.S., published a landmark paper titled "The compound nature of the action current of nerve as disclosed by the cathode ray oscillograph" (Erlanger et al., 1924). In this paper, they built on technological advances (Gasser and Erlanger 1922) to demonstrate, for the first time, that the compound action potential evoked by electrical stimuli was composed of distinct 'peaks' with different time courses. This, and subsequent pioneering work, which included determining that conduction velocity is intimately related to axon diameter and the functional significance of peripheral neurons, earned Erlanger and Gasser the 1944 Nobel Prize in Physiology or Medicine (2023).

It had long been known that there are different sizes of peripheral nerve fibres within nerve cables and that this would have implications for physiology. The idea that axon diameter could be related to conduction velocity, for instance, had been suggested by Gustaf Göthlin in Uppsala, Sweden (Gothlin 1907) over a decade before Erlanger and Gasser's discoveries. However, up until the technological advances pioneered by Gasser, who combined signal amplification with adapted cathode-ray valves, it had not been possible to visualise the time course of action potentials. In the 1924 paper, performed using their new equipment to record from the exposed phrenic and sciatic nerves of the dog and frog respectively, they described three sequential peaks of action potentials termed, in order of increasing latency, alpha, beta and gamma (Erlanger et al., 1924).

Subsequently these three fastest peaks were described as belonging to an A group. Later, using higher amplification and slower sweep speeds, they also demonstrated the presence of further longer latency elevations, called B (later added to the A group and termed Aδ) and at the longest latency C (Erlanger and Gasser 1930) (Fig. 1). They also showed that there was a relationship between conduction velocity, axon diameter, and the 'medullation' (myelination) of nerve fibres (Gasser and Erlanger 1927, Gasser 1941). These and further studies suggested a classification of distinct groups of nerve fibres each with its own conduction velocity and axonal diameter as well as after-potential duration and threshold for stimulation. The peaks present in the dorsal root correspond to what we term in sensory nerves Aβ-, Aδ-, and C-fibres (the Aα peak is also seen in the dorsal roots but is only present in muscle nerves and corresponds to proprioceptors; the Aα and Aγ peaks in the ventral root correspond to α-motor neurons and γ-motor neurons, respectively).

While this classification was, for various reasons, not felt to be ideal, including by Gasser (Gasser 1941), it raised the hope that the different classes of fibres, determined by their velocity and axonal diameter, would match with distinct functional roles. Indeed, to highlight the importance of a functional-physiological-anatomical classification Gasser, citing Zotterman (Zotterman 1939) in a review paper entitled "The classification of nerve fibers" wrote:

'*In as simple an event as pricking the skin of the finger with a needle there is first a short burst of impulses carried in fibers conducting at 90 m or more per second. Then there follow impulses at other velocities, many at about twenty meters per second; and finally there is a trail of impulses at about one meter per second. Before any of the last mentioned group arrives at the centers, a complex neurological event has taken place— the withdrawal of the hand; and the sensation of pricking has been appreciated. The sensation aroused by the slow fibers is still, however, that of pain indistinguishable qualitatively from the pain already felt. But in its setting it has a stinging, irritating character. It can be relieved by rubbing the spot, that is, it may be inhibited by sending into the central nervous system a flood of impulses carried in rapidly conducting fibers.*'

To investigate the potential association between fibre size and velocity with function, Erlanger and Gasser developed methods to differentially block nerve fibers, including compression/asphyxia and cocaine (Gasser and Erlanger 1929). They elegantly described 'block' of small through to large, and large through to small fibres, following administration of cocaine and pressure block, respectively. In doing so, they explained the opposite sequence of differential loss of motor and sensory functions through application of cocaine (sequentially pain, warmth, cold, touch and motor) and compression (sequentially motor, touch, cold, warmth and pain). This also allowed them to link perception with anatomy and physiology. Their classification of nerve fibres by velocity, axonal size, and function was so far reaching that it remains relevant and widely used to this day (Table 1). Recent developments suggest however, that now, 100 years later, a revision of their canonical classification is required.

The recognition of individuals with rare lesions and, more recently, advances in genetics/RNA sequencing suggest that the Erlanger and Gasser classification requires modification to account for the diversity of fibre types found in humans and other mammals. One further technological development that has advanced this argument, by linking nerve physiology and perception, is single unit afferent recording using microneurography.

The technique of human microneurography, developed by Karl-Erik Hagbarth and Åke Vallbo (Hagbarth and Vallbo 1967, Vallbo 2018), allows for recordings from single axons in the dorsal root or peripheral nerve. These recordings can be correlated with psychophysical observations in humans using similar stimulus parameters and involved detailing the functional properties of cutaneous and proprioceptive sense organs. Microneurography involves the percutaneous insertion of an insulated tungsten micro-electrode, typically 200 μm in diameter with an electrode tip of ~5 μm, towards a limb or facial nerve in an awake and attentive subject. To enable recording of single afferents, once a nerve fascicle is impaled the electrode is carefully manipulated to identify individual fibres with a defined cutaneous or deep (e.g., intramuscular) receptive field.

Microneurography was a major methodological advance in the study of human cutaneous sensation by allowing the minimally invasive determination of functional stimulus–response properties of afferent types and subtypes. Furthermore, by correlating neural firing to read-outs of sensory performance or perception (e.g., pain or pleasantness ratings), obtained either during recording or using identical stimuli at another time point, helped determine the role of identified afferent types, or populations of afferents, in perception. Further insights into the perceptual roles of defined afferents were made possible by combining microneurography with the related method of intraneural microstimulation (Torebjörk et al.,

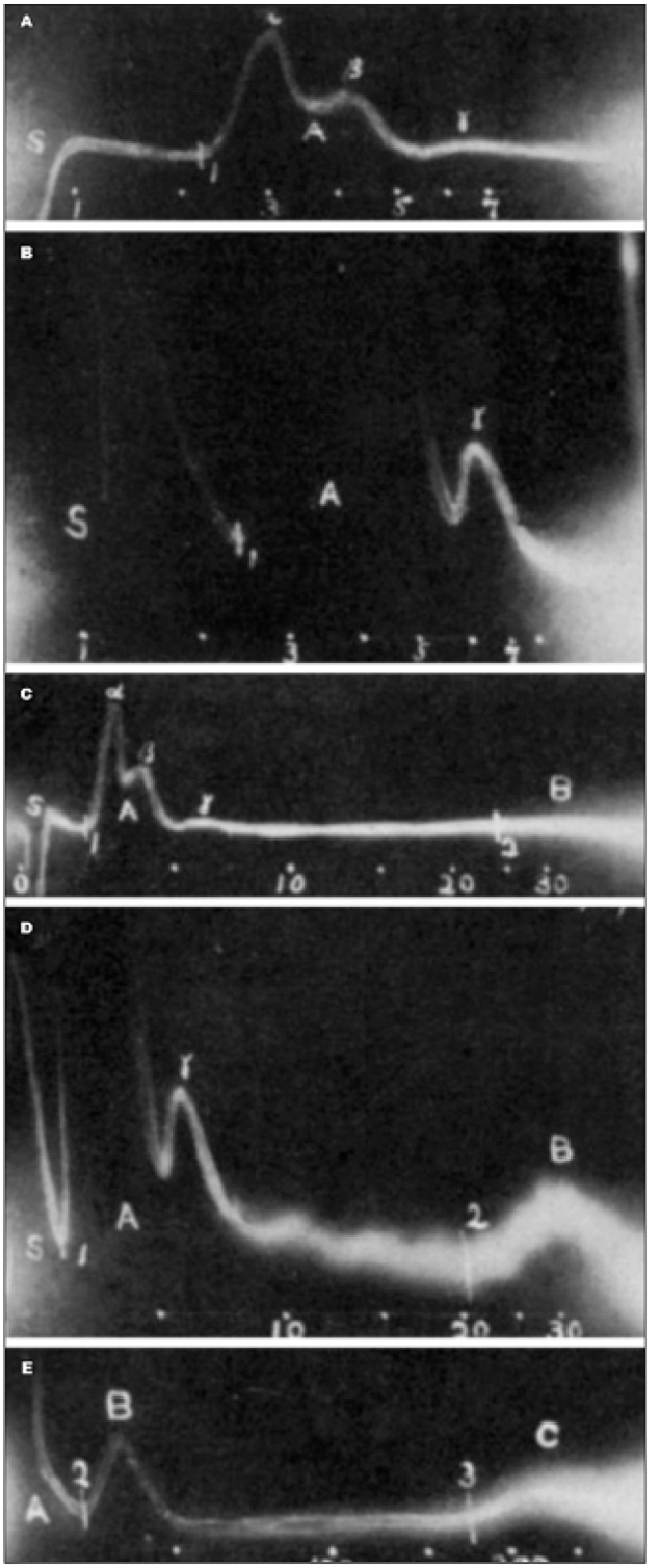

Fig. 1. Pictures of Erlanger and Gasser's oscilloscope recordings from the bullfrog sciatic nerve demonstrating distinct peaks of electrically evoked neural responses. (A) A-fibre peaks with separations showing the α, β and γ sub-peaks. (B) Same as (A) but with extended timebase revealing a B peak (subsequently named Aδ). (C) Same as (A) but with higher gain revealing the distinct γ peak. (D) Same as (C) but with longer timebase revealing a distinct Aδ peak. (E) Greatly extended timebase revealing a distinct C-fibre peak. Figure originally published by Erlanger and Gasser (1930) and reproduced with permission from the publisher.

1987), during which small stimulating currents are applied through the same electrode used for recording to stimulate that recorded afferent. Microneurography has unlocked a physiological and perceptual understanding of the basis of cutaneous sensation.

The remainder of this review will focus on research that has established the presence of a system of slowly conducting C-fibres found in animals and humans that are exquisitely responsive to gentle touch – 'slow touch' – as well as more recent evidence indicating that humans, like other mammalian species, are equipped with high threshold mechanoreceptor afferent fibres that have conduction velocities in the Aβ range. The title of the review includes the term ultrafast pain. The choice of the prefix 'ultrafast' is used to avoid nomenclatural ambiguity where Aδ-fibre pain is widely referred to as "fast" pain in the literature.

2. Questioning the canonical classification

2.1. Slow touch

2.1.1. Early discoveries

In 1939, Zotterman (Zotterman 1939) recorded from mechanoreceptors in cats' saphenous nerves which responded to light stroking of the skin. In addition to an early response following the tactile stimulation, some of the recorded spikes appeared with a long delay and had low amplitudes. From this, he suggested that the long-latency spikes must originate from unmyelinated low-threshold mechanoreceptors (C-LTMRs). This observation has subsequently been supported by the confirmation of C-LTMRs in the hairy skin of many kinds of mammals (Douglas and Ritchie 1957, Bessou et al., 1971, Iggo and Kornhuber 1977, Kumazawa and Perl 1977, Leem et al., 1993, Rukwied et al., 2020).

With the advent of microneurography (Hagbarth and Vallbo 1967), it was possible to search for C-LTMRs in humans. They were not found in humans until fifty years following Zottermaṅs discovery, when Johansson and colleagues recorded from one C-LTMR in the infraorbital nerve in the human face (Johansson et al., 1988). Soon thereafter, Nordin recorded from several C-LTMRs from the supraorbital nerve (Fig. 2) (Nordin 1990), and Vallbo and colleagues found them in the antebrachial cutaneous nerve of the forearm (Vallbo et al., 1993).

2.1.2. C-LTMRs signal pleasant touch and project to insular cortex

Zotterman originally suggested that C-LTMRs have a role in signalling tickling sensations and this view was reiterated by Nordin. Zotterman postulated that based on the capacity of gentle hair movements to stir activity in cat C-LTMRs – an effect that was reduced, or abolished, when the cat fur was moistened with water, for instance; and a comparable experience in everyday life where gentle stroking of the hairs elicits a tickling (or itching) sensation that disappears when the skin is moistened. However, a problem in ascribing perceptual correlates and the functional role of human C-LTMRs is that low-threshold large myelinated fibres are always activated in parallel. A way forward appeared some 30 years ago when one of us (author J.C.) described the case of Ian Waterman (Cole, 1995), a previously healthy 19-years-old male who suddenly became sick with a gastric infection. He immediately became wobbly and weak and unable to stand. Within days he lost all sense of proprioception or touch below the level of the cranial nerves (Cole and Sedgwick 1992). Further examination showed that he had a severe sensory ganglionopathy (sensory neuronopathy syndrome (Sterman et al., 1980)) with a complete loss of Aβ-fibres, partial loss of Aδ-fibres, but with sparing of C-fibres. About the same time as Ian Waterman was diagnosed, we met another patient (initials G.L.) who also had sensory neuronopathy syndrome (Cooke et al.,

Table 1
Canonical Erlanger and Gasser classification of fibre types in sensory peripheral nerves.

Fibre type	Function	Average fibre diameter (μm)	Average (range in parentheses) conduction velocity (m/s)
Aα	Primary muscle spindles, Golgi tendon organs	15	100 (70–120)
Aβ	Cutaneous touch and pressure afferents	8	50 (30–70)
Aδ	Cutaneous temperature (cold) and 'fast' pain	<3	15 (12–30)
C	Cutaneous pain ('slow' pain) and temperature (warmth and cold)	1	1 (0.2–2)

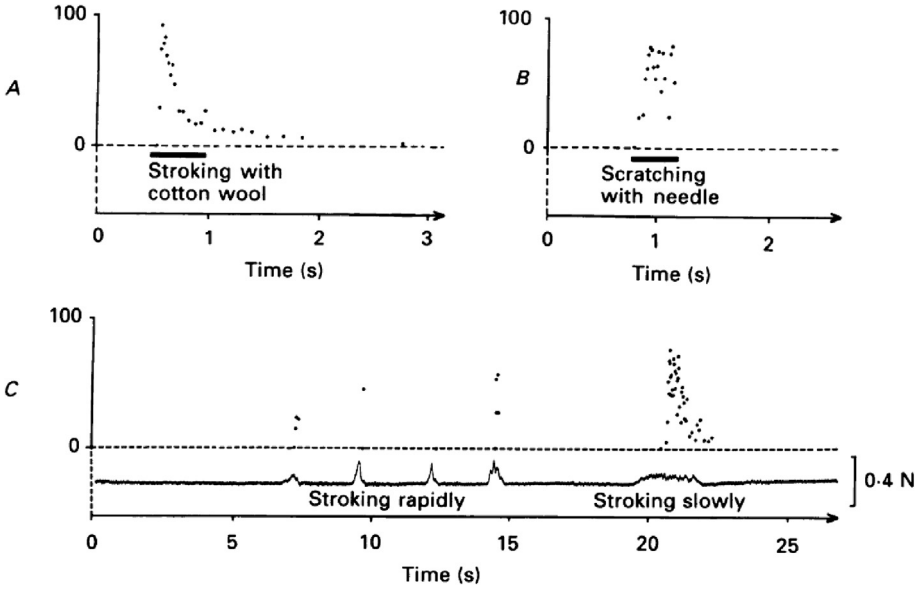

Fig. 2. Results from one of the first recordings from a human C-LTMR showing characteristic firing patterns in response to stroking stimuli. (A) Stroking with cotton wool results in a vigorous response, followed by an after-discharge in this trial. (B) For the same unit, scratching with a needle does not yield higher firing rates compared to cotton wool. (C) Effects of stroking at different velocities with a blunt probe attached to a force transducer. Note that a slow stroking movement (right), despite the lower force applied, is a more effective stimulus than faster ones. Adapted from (Nordin 1990) with permission from the publisher.

1985). The two deafferented subjects provided an opportunity to test the effect of pure C-LTMR stimulation without parallel stimulation of Aβ-fibres. Both participants said that they had lost all sensation of touch when they became ill. This was a surprise since their C-fibres remained intact, as indicated by preserved temperature sensibility (Cole et al., 2006) and evidence from nerve biopsy (Forget and Lamarre 1995), and we therefore assumed that they should also have intact C-LTMRs. To examine if they had any residual tactile function, we designed a two-alternative forced-choice (2-AFC) test. We stroked with a soft brush during one of two intervals and the patients had to choose during which of the two intervals they believed we had applied the brushing. In 2-AFC testing they were close to 100% correct for testing on the forearm (Olausson et al., 2002), a skin area densely innervated by C-LTMRs (Vallbo et al., 1999, Olausson et al., 2008). However, they performed at a chance level for testing on the glabrous skin of the hand, a skin area sparsely innervated by C-LTMRs (Watkins et al., 2021). When we asked them to describe what they felt, both said that they would not call it a typical touch sensation but instead a weak and somewhat pleasant sensation with no thermal or pain components. They reported no tickling sensation contradicting Zottermańs hypothesis (Zotterman 1939). Further testing in G.L. and I.W. showed that they have severe difficulties in localizing soft brush stroking to the extent that they mis-localize brush stroking on the arm as being on the leg and vice versa (Olausson et al., 2008). In functional magnetic resonance imaging (fMRI), after selective C-LTMR stimulation by means of slow stroking of the skin, both G.L. and I.W. had activation of the posterior insular cortex, but no activation of the somatosensory cortices (Olausson et al., 2002, Olausson et al., 2008). In contrast, in healthy control subjects we find activation of the somatosensory and insular cortices (Olausson et al., 2002, 2008). From this, we suggest that human C-LTMRs project to the insular but not to the somatosensory cortices (Olausson et al., 2002, 2008). In addition, following ischemic stroke affecting the opercular-insular cortex, there is impairment in the perception of gentle touch (Kirsch et al., 2020).

A recurrent observation from microneurography is that C-LTMRs respond well to slow stroking of the skin (Fig. 2) (Nordin 1990, Vallbo et al., 1993). To study this in detail, we used a soft brush attached to a robotic stimulator that stroked over the skin with precise control of velocity and force. We found that the C-LTMRs respond particularly well to stroking in the range of 1–10 cm/s, whereas they respond less to slower or faster brush stroking. In contrast, the different types of myelinated afferents respond more vigorously the faster the stroking (Loken et al., 2009). In psychophysical testing the subjects rate brush stroking in the range of 1–10 cm/s as more pleasant than slower or faster stroking, and there is a robust positive correlation between firing frequency of C-LTMRs and pleasantness ratings. There is no such correlation for the myelinated afferents.

In microneurographic experiments, C-LTMRs are routinely searched by stroking with the experimenteŕs hand, delivering both tactile and temperature cues. To systematically study this, we used the robotic stimulator in (Nordin 1990) and replaced the soft brush

with a Peltier element with controllable temperature. We replicated the tuning to stroking in the 1–10 cm/s velocity range, and we also found that the C-LTMR response was most vigorous at a stimulus temperature of 32 °C with weaker responses at 18 and 42 °C (Ackerley et al., 2014). We concluded that C-LTMRs are tuned to respond to a stimulus with the characteristics of a human caress.

We have also examined participants with an opposite type of denervation compared to I.W. and G.L. These have hereditary sensory and autonomic neuropathy type 5 (HSAN-V) with congenital degeneration of C-fibres and to a lesser extent Aδ-fibres and sparing of Aβ-fibres. These participants provide an opportunity to study how touch is perceived and processed without C-LTMR activation. They have a congenital pain insensitivity with painless fractures, Charcot joints, and a high prevalence of carpal tunnel syndrome (Minde 2006, Ridderstrom, Svantesson et al., 2020). When tested in the laboratory, they perceive stroking with a soft brush as less pleasant than control subjects (Morrison et al., 2011). On a group level, they perceive slow stroking (3 cm/s) as equally pleasant as fast stroking (30 cm/s). This is rarely observed in groups of neurologically intact participants (Morrison 2016, Croy et al., 2021) who perceive slow stroking as more pleasant than fast stroking. Lastly, in contrast to control participants and the Aβ-denervated subjects I.W. and G.L, those with HSAN-V do not activate the posterior insular cortex in response to brush stroking (Morrison et al., 2011).

2.1.3. Human-to-human touch

It is a robust finding that slow stroking with a soft brush is a pleasant stimulus that activates C-LTMRs. What about naturalistic touching one encounters in daily life? To study this, participants were instructed to stroke the arm of a mannequin as they would caress their partner or a close friend. When measuring the speed of the hand movements the participants use speeds faster than the C-LTMR optimal range of 1–10 cm/s (Croy et al., 2016). However, when the participants were asked to bring their partner or a close friend and stroke their forearm, they all stroked with velocities in the C-LTMR optimal range (Croy et al., 2016).

Touch is an effective means of communicating emotions (Hertenstein et al., 2009). To study the physical features of interpersonal touch communication, McIntyre and colleagues invited couples to the lab, assigning one as the sender and the other as the receiver. The instruction to the sender was to communicate the meaning of one of the words: attention, love, happiness, calming, sadness, or gratitude. The experiment was video-recorded, and a set of "standardized" gestures was constructed (McIntyre et al., 2022) which were effective in communicating the meaning of the different words. The attention gesture is characterized by firm tapping on the skin, love is slow and gentle stroking, happiness is light and rapid tapping, calming is firm stroking, sadness is holding still, and gratitude is patting. These physical features were then applied during microneurography recordings, and the C-LTMRs display a preference for stroking and holding stimuli, which are also rated as most pleasant (McIntyre et al., 2022, Xu et al., 2023). Further studies using machine-learning found that information from certain types of myelinated afferents is particularly informative in discriminating between the different physical features (Xu et al., 2023). The information from C-LTMRs is less useful for discrimination, likely due to their high response variability from trial to trial. Thus, a dual tactile system may exist: one performing sensory functions relying on Aβ-LTMR inputs and the other shaping the valence of those inputs likely signalled by C-LTMRs. However, it should be emphasised that the valence of touch is dependent on contextual factors, such as who is doing the touching (Gazzola et al., 2012). This suggests in turn that information from Aβ- and C-LTMRs is integrated. Some of this may well occur already at the level of the spinal dorsal horn (Marshall et al., 2019) but cortical factors are likely to be involved too.

C-LTMRs have also been implicated in pain modulation in humans and animals, both in pro- and anti-nociceptive roles (Nagi and Mahns 2013, Liljencrantz et al., 2017). While the morphology and organization of C-LTMRs in the primate spinal cord remain unknown, evidence in rodents suggests that they are well-suited to play this bidirectional role with a complex structure of endings in the dorsal horn enabling access to both excitatory and inhibitory circuits and affording a capacity for a wide range of synaptic plasticity mechanisms (Larsson and Broman 2019).

2.2. Fast pain

2.2.1. Early discoveries

Gasser and Erlanger (Gasser and Erlanger 1929), as well as textbooks in physiology or medicine, state that nociceptive input is signalled at a slower velocity than touch. However, this prompts the question: why should it be important to react more rapidly to touch than to pain? The more so since it has for long time been accepted that there are nociceptors belonging to the Aβ category in non-human mammals, including non-human primates (Treede et al., 1998, Djouhri and Lawson 2004). The number of Aβ-nociceptors in these animals is substantial; in cats, around one-third, and in mice, rats, and guinea pigs, more than half of the myelinated nociceptors conduct in the Aβ range (Burgess and Perl 1967, Burgess et al., 1968, Koltzenburg et al., 1997, Djouhri and Lawson 2004). In humans, on the other hand, nociceptive afferents have been thought to exclusively be Aδ- or C-fibres.

A few years ago, Nagi and colleagues recorded from a class of high-threshold afferents in human skin that encode the intensity of pinprick stimulation (Nagi et al., 2019). The firing frequency of these afferents correlated with pain intensity ratings demonstrating that they are nociceptive afferents, presumably signalling pinprick-type pain (Fig. 3). Consistently, intraneural microstimulation of these single afferents produce sharp, pinprick pain (Nagi et al., 2019). These pinprick nociceptors have a similar conduction velocity to fast-conducting touch fibres, demonstrating that they are Aβ afferents. It seems reasonable to assume that pinprick nociceptors have a role in signalling rapid limb withdrawal responses to painful stimuli. The nociceptive reflex comprises short- or long-latency, or dual, EMG responses, and we found that short-latency responses are just as painful as long-latency responses (Thorell et al., 2022). Further, the reflex can be abolished by a preferential large-fibre conduction block, suggesting a contribution of fast-conducting afferents in shaping human nocifensive behaviours (Thorell et al., 2023).

Recently, it was found that in addition to pinprick nociceptors there is another type of afferent that conveys pain evoked by hair pulling (Bouchatta et al., 2023). These afferents surround hair follicles and respond vigorously to the pulling of hairs, both terminal and vellus types. There is a correlation between firing in these neurons and pain intensity ratings, demonstrating that they are nociceptors. The hair pull nociceptors have similar conduction velocity to touch afferents, so these hair pull nociceptors appear to be yet another class of Aβ-nociceptors.

2.3. Implications for clinical neurophysiology

The main purpose of the present paper is to refine and extend the classification of peripheral sensory nerves according to recent research. While it is straightforward to classify nerves based on their conduction velocity, the challenge lies in classifying the perceptual correlates of the activation of diverse types of afferents. This is in part because perception is dependent on central processing and under top-down and bottom-up influences, and in part because not all classes of receptors and afferents serve a clear, singular perceptual correlate.

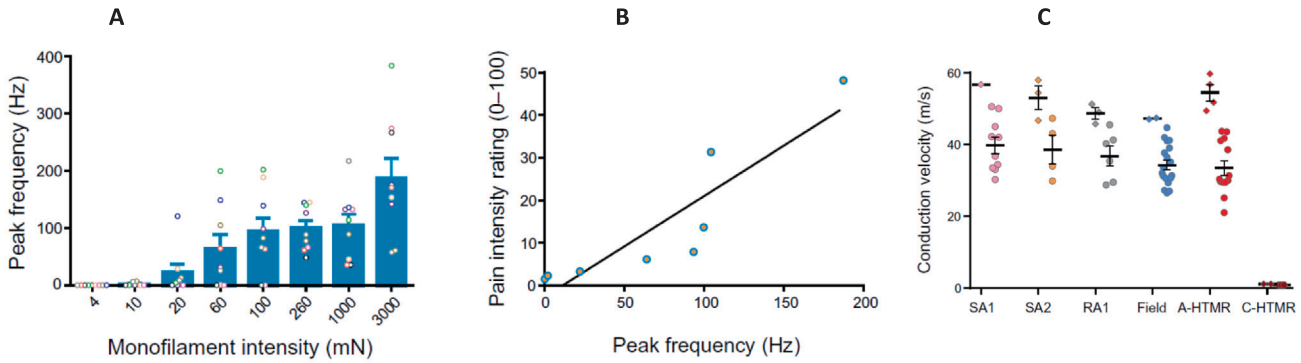

Fig. 3. Humans are equipped with nociceptors with very fast conducting afferents. (A) Peak discharge rates of human A-fibre high-threshold mechanoreceptors (A-HTMRs) in response to monofilament stimulation. The data show individual and average (±SEM) responses of nine A-HTMRs (≥30 m/s) to 5-s monofilament stimulation at eight different indentation forces. (B) Psychophysical pain ratings as a function of neural discharge in A-HTMRs. A comparison of the average peak discharge rates of nine A-HTMRs and average psychophysical pain ratings for skin indentations (eight forces, 4 to 3000 mN) revealed a significant positive correlation (Pearson r = 0.8944, R^2 = 0.8, P = 0.0027). (C) Conduction velocities of HTMRs and LTMRs to surface electrical stimulation (and monofilament tapping in case of one HTMR, conducting at 30 m/s). The data show individual and average (±SEM) conduction velocities of single afferents from peroneal (circles) and radial (diamonds) nerves. Conduction velocities of peroneal A-HTMRs (33.5 ± 2.1; n = 13) were statistically indistinguishable from peroneal A-LTMRs [SA1: 39.8 ± 2.3, n = 10; SA2: 38.6 ± 4.0, n = 4; RA1: 36.8 ± 2.8, n = 6; field: 34.3 ± 1.3, n = 18; F(4,46) = 1.70; P = 0.17, one-way analysis of variance (ANOVA)]. All three peroneal C-HTMRs were conducting at 0.9 m/s. In comparison to the peroneal nerve, conduction velocities of A-fibre types were faster in the radial nerve as expected (A-HTMR: 54.5 ± 2.4, n = 4; SA1: 56.8 m/s, n = 1; SA2: 53.0 ± 3.3, n = 3; RA1: 48.7 ± 1.6, n = 3; field: 47.3 ± 0.2, n = 2). SA, slowly adapting. RA, rapidly adapting. Adapted from (Nagi, Marshall et al., 2019).

For the perception associated with pure C-LTMR activation, we have been dependent on a very small cohort of participants with a selective loss of large myelinated sensory afferents, but with preserved small-fibre function. What appears clear is that substantial activation of these afferents, including spatial and temporal summation (which may be important), via slow brushing of hairy skin does not lead to a stimulus sufficient to alert these participants to it. The C-LTMR related activation only reaches a conscious level, when participants are attending to the stimulus and compelled to make a two-choice forced decision. Under these conditions, a vague perception of pleasantness is volunteered, rather than a typical touch sensation. The C-LTMR related perception can be localized, although poorly (Olausson et al., 2008), and is not as intense as the touch induced pleasantness experienced by control subjects. This is also suggested by results from subjects with HSAN-V who lack small but retain large fibres (Minde et al., 2009). This implies that some perceptions are the result of interaction between different classes of afferents. C-LTMRs may have a role in instructing and facilitating afferent information also conveyed through Aβ light touch afferents, and the subsequent percept, rather than being perceived themselves. This, in turn, suggests there must be cross-talk between these slow and fast touch systems. Marshall and co-workers have data suggesting that some of this integration may occur in the segmental dorsal horn before being projected rostrally to insula and sensory cortex, probably via the dorsal column (Marshall et al., 2019). Yet unknown is how this cross-talk is integrated, with differing time courses of impulse propagation, one through C-fibres and the other through Aβ, and with differing tuning properties to similar stimuli. It seems unlikely, however, that this is all. For example, a stroke which might be pleasant in one situation, from a family member, would be unpleasant if unwanted from a stranger. The integration of social situation, memory, and expectation may be something arising in the insula and other areas within the brain top-down and dependent on context. Pleasant sensation can also be perceived in areas with few C-LTMRs like the palm of the hand (Watkins et al., 2021), though there the relationship between active exploratory touch and passive received touch may be of relevance.

The demonstration of Aβ nociceptors, as well as nociceptive input conveyed through C- and A-δ fibres, raises the question as to how these differing classes signal different stimuli and, hence, how they are felt differently. As we suggested above, a fast-signalling pathway for externally produced high-threshold mechanical activation in the skin, to alert one to action earlier and to act as the afferent limb of flexion withdrawal reflex, has clear evolutionary advantages. The loss of such a protective reflex in response to a sharp stone in the shoe or standing on a pin may be an important risk factor for neuropathic ulceration. We have also shown that participants without Aβ sensory afferents have reduced pinprick pain, whereas those with reduced small fibres (HSAN-V) have preserved pinprick pain (Nagi et al., 2019). Collectively, these findings prompt a reevaluation of neurological views that: pinprick examination specifically assesses small-fibre function; pure large-fibre neuropathies do not have pain disturbance; painful neuropathies imply small-fibre involvement.

These observations on Aβ-nociceptors do not preclude the role of small-diameter nociceptors in pain signalling. Indeed, their discovery underscores the fact that nociceptors can be found in all Erlanger and Gasser skin nerve fibre classes. Evoked cortical potentials recorded from the scalp in response to noxious heat stimulation delivered by a laser to the skin of the face or limbs show latencies in keeping with transmission along Aδ pathways (Kakigi et al., 1991, Lefaucheur et al., 2001, Tran et al., 2001, Caetano et al., 2010). Indeed, latencies for pure noxious heat stimulation are longer than those elicited using pinprick stimulation (Iannetti et al., 2013). Therefore, Aδ-nociceptors in humans likely have functional roles and perceptual correlates important in the detection and sensing of heat pain (for reviews encompassing evidence in human and nonhuman species see (Djouhri and Lawson 2004, Schepers and Ringkamp 2010)). C-fibre nociceptors include differing categories of afferents, including those related to thermal pain, itch, and neurogenic inflammation, some of which may be mediated through chemicals, including neurotransmitters, and aspects of noxious pinprick. Their complex firing patterns and prolonged discharge suit them for longer-term signalling.

Different classes of sensory afferents signalling nociceptive input may explain some of the differing types of neuropathic pain. Burning pain, which is often prolonged and unpleasant in character, is likely conveyed primarily through the C-fibre system while

stabbing, stinging, or lightning pains might reflect myelinated, including Aβ range, nociceptor activation (for arguments implicating a role for Aβ fibres in causing pain, see (Truini et al., 2013)). Of course, though, neuropathies more often involve more than one fibre type and may affect mixtures of different afferents. Pure lines of afferent-to-percept may not always be the case, as in mechanical allodynia where LTMRs are presumed to interact with segmental nociceptive inputs. However, sensitization of Aβ-nociceptors (e.g., of hair pull nociceptors so that they now respond also to hair deflection) could, at least partly, account for mechanical allodynia without it being necessary to invoke more complex spinal mechanisms.

Lastly, the demonstration of Aβ-nociceptors may explain why nerve conduction studies are uncomfortable, unpleasant, and, for some, painful. Stimulation is usually above the sensory threshold but below the level at which Aδ and C fibres within a peripheral nerve are activated by electrical stimulation. The unpleasantness might be due to high currents at the skin site activating nociceptors, but phenomenologically, the perception is felt as being more widespread and more in the distribution of the nerve stimulated. It remains possible that supramaximal stimulation of Aβ-LTMRs in a peripheral nerve might lead to a volley which spills over to interact with nociceptive afferents. But now another, simpler explanation may be that nerve conduction studies activate Aβ-nociceptors.

It is straightforward to classify nerves based on their conduction velocity, and conduction velocity in turn is a useful marker of nerve damage. However, the classical relation between nerve conduction and function has become blurred. Touch can be signalled by the slowest, and pain can be signalled by the fastest of afferent nerve fibres. Recent advances in single cell RNA-sequencing of human dorsal root ganglia from deceased donors suggest another type of classification based on the molecular expressions of the afferents (Nguyen et al., 2021, Tavares-Ferreira et al., 2022, Jung et al., 2023). Afferent types within the dorsal root ganglion are classified according to which genes are transcribed into messenger RNA, resulting in clusters of neurons with a common 'transcriptomic' fingerprint. This can be related to the soma size of the dorsal root ganglia cell (small soma size reflects unmyelinated afferents; large soma size reflects large, myelinated afferents). However, a disadvantage with molecular classification is that the relation between molecular features and function is unknown (Kupari and Ernfors 2023). Perhaps an integrated classification system based on molecular expressions, measured through single cell RNA-sequencing, and electrophysiological response properties, measured with microneurography, could serve as a basis for a refined taxonomy of the peripheral afferent nervous system (Zeng and Sanes 2017, Yu 2023).

Conflict of interest statement

None of the authors have potential conflicts of interest to be disclosed.

CRediT authorship contribution statement

Håkan Olausson: Writing – review & editing. **Andrew Marshall:** Writing – review & editing. **Saad S. Nagi:** Writing – review & editing. **Jonathan Cole:** Writing – review & editing.

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