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NEUROSCIENCE

REVIEW

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The Effects of Ageing on Tactile Function in Humans

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Abstract—Ageing is accompanied by a steady decline in touch sensitivity and acuity. Conversely, pleasant touch, such as experienced during a caress, is even more pleasant in old age. There are many physiological changes that might explain these perceptual changes, but researchers have not yet identified any specific mechanisms. Here, we review both the perceptual and structural changes to the touch system that are associated with ageing. The structural changes include reduced elasticity of the skin in older people, as well as reduced numbers and altered morphology of skin tactile receptors. Effects of ageing on the peripheral and central nervous systems include demyelination, which affects the timing of neural signals, as well as reduced numbers of peripheral nerve fibres. The ageing brain also undergoes complex changes in blood flow, metabolism, plasticity, neurotransmitter function, and, for touch, the body map in primary somatosensory cortex. Although several studies have attempted to find a direct link between perceptual and structural changes, this has proved surprisingly elusive. We also highlight the need for more evidence regarding age-related changes in peripheral nerve function in the hairy skin, as well as the social and emotional aspects of touch.

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Keywords: ageing, touch, peripheral nervous system, central nervous system, affective touch, skin, human.

INTRODUCTION

It is well-known that ageing is associated with reduced sensitivity in hearing, vision, taste, smell, proprioception, vestibular function, and touch. For all these modalities the decline in sensory functions is typically observed above the age of 60 years. However, the sensory decline is not general across sensory modalities and can affect one modality whilst sparing others (Cavazzana et al., 2018). Among the senses, ageing of the touch system is one of the least studied, particularly regarding the social and emotional aspects of touch. Tactile impairment may have a profound impact on the quality of life, since touch is crucial not only for handling objects and detection of stimuli, but interpersonal touch is also crucial for strengthening bonds and communicating emotions (Hertenstein et al., 2009; McGlone et al., 2014; McIntyre et al., 2019).

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Abbreviations: BDNF, brain-derived neurotrophic factor; RA1, rapidly adapting type 1; RA2, rapidly adapting type 2; SA1, slowly adapting type 1; SA2, slowly adapting type 2; TrkB, tyrosine receptor kinase.

CHANGING PROPERTIES OF THE SKIN

Skin ageing is characterised by wrinkles and loss of firmness and elasticity (Zhang and Duan, 2018) which may negatively influence the skin-neural coupling. However, the evidence is mixed as to what extent the physical properties of the skin contribute to the decline in touch discrimination (Skedung et al., 2018; Aimonetti et al., 2019). Many elderly people have a good capacity to discriminate between different levels of surface roughness despite the cutaneous condition, and the more important mechanisms for touch impairments with age are likely to be found within the cutaneous nervous system (Skedung et al., 2018).

THE PERIPHERAL NERVOUS SYSTEM

The functionally most crucial factors for the decline of discriminative touch with age are likely to be found within the peripheral nervous system including skin receptors, mechanotransduction processes, and nerve fibres. Tactile afferents innervating the skin are pseudounipolar neurons with the cell body in the dorsal root ganglia or trigeminal ganglia. The peripheral part of the tactile afferent projects to the skin and the central part connects to the dorsal horn of the spinal cord (or the brainstem for the trigeminal nerve). The long peripheral axon innervates specialised end organs

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(Merkel, Ruffini, Meissner, and Pacinian types) or ends in free nerve endings in the dermis and epidermis (Lumpkin and Caterina, 2007), which either surround hair follicles or terminate in the superficial layers of the skin. The specialised receptor endings may serve to mechanically magnify or filter the forces imposed on the skin. Animal studies have shown that the brain-derived neurotrophic factor (BDNF) and tyrosine receptor kinase (TrkB) are important for the development and function of mechanoreceptors (Botchkarev et al., 1999; LeMaster et al., 1999; Cabo et al., 2015).

It has long been known that there is an overall decrease in the number of nerve fibres in the dermis and epidermis with age (Verdu et al., 2000; Besne et al., 2002; Chang et al., 2004). There is also a well-known decrease in nerve conduction velocity and amplitude of the compound action potential of sensory neurons with age (Bouche et al., 1993; Palve and Palve, 2018). A number of histological studies have counted touch-sensitive peripheral neurons in humans and reported age-related reductions in myelinated fibres in the spinal roots (Corbin and Gardner, 1937) as well as evidence of degeneration of both myelinated and unmyelinated fibres in peripheral nerves (Ochoa and Mair, 1969; Tohgi et al., 1977). Recently, a pilot study on human biopsies described prevalence of toxic neuroproteins during ageing which may explain some dysfunctions (Akerman et al., 2019). However, more detailed studies on the mechanisms of age-related changes in individual mechanosensitive afferent neurons and their axonal transmission of action potentials are scarce. For example, to our knowledge, there are no single afferent recordings (microneurography) from aged skin in humans.

Mechanotransduction

The primary mechanotransduction process for many touch-sensitive neurons has recently been discovered in an animal model. Skin deformation is translated into action potentials in the nerve via stretch-sensitive ion channels called Piezo2 (Ranade et al., 2014; Woo et al., 2014; Chesler et al., 2016). Piezo2 channels open in response to mechanical forces applied to the cell, allowing charged ions to enter, triggering action potentials (Wang et al., 2019). In the mouse, Piezo2 expression is found in the nerve endings of several types of touch-sensitive primary afferent neurons, including those that terminate around hair follicles, in Meissner corpuscles in the glabrous skin, and in Merkel cells that are found in both hairy and glabrous skin (Ranade et al., 2014).

Very little is known regarding age-related changes in mechanotransduction. One human study measured multiunit electrical activity in touch-sensitive primary afferent neurons in the median nerve, comparing their responses to mechanical stimulation of the skin and electrical stimulation of the nerve. They reported an age-related decline in the ratio of mechanical to electrical response (Schmidt and Wahren, 1990; Schmidt et al., 1990). This could be due to less reliable transduction in the ageing touch system, or due to the loss of receptor endings.

Receptor endings

In the glabrous skin, thickly myelinated, Aβ touch-sensitive primary afferents are associated with four different receptor endings, as described earlier. Mechanical stimulation of Merkel cells causes a continuous irregular firing of action potentials, and the Aβ nerve fibres that are connected to the Merkel cells are electrophysiologically termed slowly adapting type 1 (SA1) afferents. Expressed in other words, the SA1 afferents connected to the Merkel cells continue to fire as long as the skin is mechanically deformed. The irregular firing pattern of the SA1 receptor is thought to be due to its morphological organisation with separate branches of the stem axon supplying the individual Merkel discs (Iggo and Muir, 1969; Lumpkin and Caterina, 2007).

Mechanical stimulation of Ruffini corpuscles causes a continuous regular firing of action potentials, and the connected nerve fibres are electrophysiologically termed slowly adapting type 2 (SA2) afferents. The regular firing pattern of the SA2 receptor also seems consistent with the morphology of the Ruffini ending, wherein an undivided axon enters the capsule and bifurcates to form an intracapsular terminal arborisation (Chambers et al., 1972). However, the regularity of discharge disappears at low firing frequencies (Wellnitz et al., 2010), which can lend ambiguity to the differentiation between SA1 and SA2 responses.

Mechanical stimulation of Meissner corpuscles causes ‘on’ and ‘off’ responses in the connected axon, and the afferents are electrophysiologically classified as rapidly adapting type 1 (RA1). Thus, the RA1 axons connected to the Meissner corpuscles respond with a burst of action potentials to the onset and offset of mechanical stimulation (Vallbo and Johansson, 1984). Pacinian corpuscles are exquisitely sensitive to vibration and are electrophysiologically termed rapidly adapting type 2 (RA2) (Vallbo and Johansson, 1984).

A number of studies examined samples from the glabrous skin of human fingers obtained during autopsy or following amputation (Cauna, 1965; Bruce and Sinclair, 1980; Bruce, 1980; Iwasaki et al., 2003; Garcia-Piqueras et al., 2019). Details in age-related degeneration of cutaneous mechanoreceptors were studied using microscopy and immunohistochemistry in human skin from those in infancy to over 90 years old. After an early developmental propagation, Merkel cells decrease steadily in number with age (Cauna, 1965; Garcia-Piqueras et al., 2019), and there is a reduction of immunostaining for BDNF and TrkB, and a decrease in Piezo2 ion channels (Garcia-Piqueras et al., 2019). Pacinian corpuscles undergo dramatic morphological changes, growing up to six times in size over most of the life span, becoming more complex (Cauna, 1965), and they do not appear to reduce in number (Cauna, 1965; Garcia-Piqueras et al., 2019). A histological study on skin samples obtained from human glabrous skin during autopsy were analysed for subjects in the age range 23–90 years (Garcia-Piqueras et al., 2019). Interestingly, the structure of the Pacinian corpuscles, including the arrangement of corpuscular components and concentric

lamellae, were similar across age groups. There were signs of loss of axonal innervation for a few Pacinian corpuscles from the older subjects, but overall the Pacinian corpuscles seem resistant to age-related degeneration.

Meissner corpuscles steadily decline in number with age (Cauna, 1965; Bruce and Sinclair, 1980; Bruce, 1980; Iwasaki et al., 2003). Compared to young people, Meissner corpuscles in older people show altered morphology (Cauna, 1965; Garcia-Piqueras et al., 2019), many lack axons (Garcia-Piqueras et al., 2019), and contrastingly, nerve endings sometimes remain after the loss of the corpuscle (Cauna, 1965). Meissner corpuscles also show less immunostaining for BDNF and TrkB with age, and there is a decrease in Piezo2 ion channels (Garcia-Piqueras et al., 2019). One important study has identified a potential role for Meissner corpuscles in age-related declines in texture discrimination (Skedung et al., 2018). They reported that some older individuals have relatively well-preserved texture discrimination compared to others, and that these high performers also had a higher density of Meissner corpuscles in the finger pad, measured using a microscope. Curiously, another study found that age-related declines in touch detection thresholds for different skin regions do not reflect the age-related reductions in Meissner corpuscle density at a group level (Bruce and Sinclair, 1980; Bruce, 1980).

In the hairy skin, both thickly myelinated Aβ and unmyelinated C afferent fibres are associated with touch-sensitive primary afferents. Hairy skin lacks Meissner corpuscles but has Field mechanoreceptors whose axons have rapidly adapting properties (RA1) (Vallbo et al., 1995; Löken et al., 2009; Nagi et al., 2019). The hair follicle afferent (HFA) constitutes another type of RA mechanoreceptor that, as the name implies, is found exclusively in the hairy skin. Pacinian corpuscles are located more remotely in the hairy skin such as in the vicinity of joints and interosseous membrane (Calne and Pallis, 1966; Iggo and Ogawa, 1977). Hairy skin is also innervated by unmyelinated low-threshold mechanoreceptors (C-LTMRs) which are typically called C-tactile fibres (CTs) in the human literature (Nordin, 1990; Vallbo et al., 1993; Wiklund Fernstrom et al., 1999; Löken et al., 2009). The authors are not aware of any studies that have systematically examined the effects of ageing on C-tactile afferents.

THE CENTRAL NERVOUS SYSTEM

There are very few mechanistic studies on the effects of ageing specifically on tactile processing. Hand representation in primary somatosensory cortex (S1) is expanded by about 40% in 60–85-year-olds, compared to 19–35-year-olds, and accompanies poorer spatial acuity in the same individuals (Kalisch et al., 2009). This is a puzzling finding that contrasts with the more typical association in younger adults between cortical map expansion and improved sensory performance, such as in string musicians (Elbert et al., 1995) and braille readers (Pascual-Leone and Torres, 1993), but may be a consequence of the reduction of intra-cortical inhibition developing with age.

More generally, the effects of ageing on the human central nervous system include weight loss of the brain, which accelerates after age 70 and is attributed to the loss of myelin and neurons, with a total loss of up to 15% of the peak brain weight by age 90. In addition, changes in cerebral blood flow and metabolism have been observed in the ageing brain (Yamaguchi et al., 1986; Goyal et al., 2017), which increases the risk of neurodegeneration. Although the specific functional consequences for touch sensation are unclear, there are cerebral vasculature and blood flow changes in the somatosensory cortex of aged mice (Li et al., 2018). Animal studies on the effects of ageing have also shown a brain-wide reduction in serotonin (Miguez et al., 1999), and in the parietal cortex, a reduction in serotonergic receptors and an increase in glutamate receptors (Wenk et al., 1989). Karrer et al. (2019) found a reduced serotonergic signal transmission in healthy ageing with evidence of preservation of 5-HT-1A compared to 5-HT-2A receptors. The authors claim this reduction may partially explain psychological age differences such as why older adults use more emotion-focused rather than problem-focused coping strategies (Karrer et al., 2019).

In rodents, there is experimental evidence of reduced synaptic functioning with age in the somatosensory system, including the S1 and S2 cortices and thalamus (Voglewede et al., 2019). For whisker stimulation, aged mice show several differences in synaptic functioning compared to younger mice. The differences include reduced ability to remodel synaptic function (plasticity) and reduced integrity of the synapses. Such deficiency may be particularly detrimental when aged mice experience novel sensory stimuli, and the brain's capacity to incorporate them is affected. Furthermore, the degeneration of the CNS with age does not seem to be due to a loss of neurons but rather damage to the myelin of the neurons. The demyelination affects the conduction velocity of the CNS neurons, which in turn disrupts the timing of the nerve signals. Indeed, there is a correlation between demyelination and cognitive decline (Moss et al., 1999).

CHANGES IN TOUCH PERCEPTION

Broadly, there are two aspects of touch sensation and perception. One aspect is the capacity to discriminate between different physical characteristics of a stimulus. For discriminative touch the rapidly conducting peripheral large myelinated afferents, the dorsal column, and the somatosensory cortices are of paramount importance (McGlone et al., 2014). Another aspect is the affective responses that can be evoked by tactile stimuli (Morrison et al., 2010). This could be feelings of calmness or joy when being touched by a loved one or feelings of disgust from an unwanted touch. The anatomical structures critical for affective touch are less known. In addition to large myelinated afferents, the slowly conducting unmyelinated peripheral afferents (C-tactile or CT) have an important role (Olausson et al., 2002; Löken et al., 2009). Stimuli of affective importance like stroking, squeezing or holding activate large-myelinated afferents and C-tactile afferents in parallel. The information from

these type of afferents is integrated at the dorsal horn (Abraira and Ginty, 2013), and transmitted to insular, orbitofrontal, superior temporal cortices, and beyond (Olausson et al., 2002; McGlone et al., 2012; Gordon et al., 2013; Davidovic et al., 2016). How affective touch is signalled in the spinal cord remains a mystery. In mice affective touch is projected in the anterolateral pathway (Choi et al., 2020) whereas in humans lesioning of the anterolateral tract does not alter affective touch perception (Marshall et al., 2019).

Discriminative aspects of tactile function are known to decline with age, including the ability to detect light touch (Newman, 1979; Bruce and Sinclair, 1980; Bruce, 1980; Thornbury and Mistretta, 1981), or vibration at different frequencies (Kenshalo, 1986; Thomson et al., 1993; Gescheider et al., 1994; Goble et al., 1996), to discriminate between different levels of surface roughness (Norman et al., 2016), or the distance between spatial features (Stevens, 1992; Stevens and Patterson, 1995; Stevens and Choo, 1996; Stevens et al., 1998; Desrosiers et al., 1999; Dinse et al., 2006), or to discriminate the direction of movement (Olausson et al., 1997; Lundblad et al., 2020). These capacities decline after around 60 years of age and this may be due to changing properties of the skin as well as neural degeneration of the peripheral and central nervous systems (Wickremaratchi and Llewelyn, 2006; Skedung et al., 2018). However, studies directly investigating these relationships have not yet established clear mechanisms for the functional decline (Bruce and Sinclair, 1980; Bruce, 1980; Escoffier et al., 1989; Cua et al., 1990; Schmidt and Wahren, 1990; Schmidt et al., 1990; Ishikawa et al., 1995; Skedung et al., 2018). Given that this functional decline is well-established, the lack of a known mechanism is a clear gap in our knowledge.

Interestingly the pleasantness of being touched has been found to increase with age above 60 years in sharp contrast to the decrease in perceived intensity of touch, and the decline in discriminative tactile functions (Newman, 1979; Bruce and Sinclair, 1980; Bruce, 1980; Verrillo et al., 2002; Guest et al., 2014; Sehlstedt et al., 2016). In 120 healthy subjects of both sexes aged 13–82 years (Sehlstedt et al., 2016), the relationship between age and psychophysical ratings of intensity and pleasantness in response to gentle stroking touch was studied (Sehlstedt et al., 2016). The results show that touch intensity ratings are negatively correlated with age consistent with age-related decline of peripheral afferent function. Perhaps surprisingly there is a positive correlation between pleasantness ratings of touch and age. Furthermore, the number of emotional words used to describe gentle touch increases with age (Guest et al., 2014). However, May et al. (2014) found no effect of age on pleasantness ratings in a narrower age range (15–55 years).

The increase in touch pleasantness in later adulthood suggests that the peripheral unmyelinated (C) tactile afferents surmised to underpin touch pleasantness are somewhat resistant to age-related degeneration, akin to the Pacinian corpuscles. Since discriminative touch mediated by large myelinated afferents declines with age (cf. above), the relative contribution of C-tactile afferents to the tactile-evoked afferent barrage will be stronger. It is possible that a relatively stronger C-tactile contribution may explain the higher pleasantness ratings with age. However another, perhaps more likely explanation is that the age-related increase in touch pleasantness is explained in psychological terms as a consequence of "longing for interpersonal touch" (Bessler et al., 2019) or "touch hunger" (Field, 2010). In other words, a reduction in the amount of interpersonal touch, which probably is more common in the elderly, may lead to increased enjoyment of touch (Sehlstedt et al., 2016). However, any explanation for the increase in touch pleasantness with ageing remains speculative and mechanistic studies are required for further understanding of the phenomenon.

The age-related decline in tactile function is well-established, but precise neural mechanisms that link physiological and perceptual changes remain elusive. There exist multiple physical and neurophysiological changes throughout the lifespan that are candidates for explaining the functional decline. The skin loses elasticity and firmness with age. In the glabrous skin of the hands, a variety of receptor endings for mechanosensitive primary afferents undergo morphological changes and decline in number. Furthermore, demyelination in both the central and peripheral nervous system occur with ageing. Despite these many observed changes, attempts to find a strong link between their progression and the decline in functional performance on tactile tasks have failed. A satisfactory explanation of the mechanism needs to consider all these changes and how their effects combine. In addition, there is remarkably little data on the effects of ageing on hairy skin receptors, and on the social and emotional aspects of touch.

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