



Review

Vascular and Neural Response to Focal Vibration, Sensory Feedback, and Piezo Ion Channel Signaling

Harald Penasso ^{1,*} , Frederike Petersen ² and Gerfried Peternell ^{3,4}

¹ Department of Integrative Physiology, University of Colorado Boulder, Boulder, CO 80309, USA

² Saphenus Medical Technology GmbH, Hauptplatz 9–13, 2500 Baden, Austria

³ Ludwig Boltzmann Institute for Traumatology, 1200 Vienna, Austria

⁴ AUVA Rehabilitation Clinic, 8144 Tobelbad, Austria

* Correspondence: harald.penasso@colorado.edu

Abstract: Focal vibration therapy seeks to restore the physiological function of tissues and the nervous system. Recommendations for vibration settings, e.g., that could improve residual limb health and prosthesis acceptance in people with amputation, are pending. To establish a physiological connection between focal vibration settings, clinical outcomes, and molecular and neuronal mechanisms, we combined the literature on focal vibration therapy, vibrotactile feedback, mechanosensitive Piezo ion channels, touch, proprioception, neuromodulation, and the recovery of blood vessels and nerves. In summary, intermittent focal vibration increases endothelial shear stress when applied superficially to blood vessels and tissues and triggers Piezo1 signaling, supporting the repair and formation of blood vessels and nerves. Conversely, stimulating Piezo1 in peripheral axon growth cones could reduce the growth of painful neuromas. Vibrotactile feedback also creates sensory inputs to the motor cortex, predominantly through Piezo2-related channels, and modulates sensory signals in the dorsal horn and ascending arousal system. Thus, sensory feedback supports physiological recovery from maladaptations and can alleviate phantom pain and promote body awareness and physical activity. We recommend focal vibration of phantom limb maps with frequencies from ~60–120 Hz and amplitudes up to 1 mm to positively affect motor control, locomotion, pain, nerves, and blood vessels while avoiding adverse effects.

Keywords: peripheral vascular disease; neuropathic pain; phantom limb pain; amputation; endothelium; local vibration; vibrotactile feedback; CRPS; vibration therapy



Citation: Penasso, H.; Petersen, F.; Peternell, G. Vascular and Neural Response to Focal Vibration, Sensory Feedback, and Piezo Ion Channel Signaling. *JVD* **2023**, *2*, 42–90.
<https://doi.org/10.3390/jvd2010006>

Academic Editor: Stefan Schob

Received: 9 November 2022

Revised: 5 December 2022

Accepted: 3 January 2023

Published: 19 January 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Touch and mechanical stimulation have been used for centuries to ease pain and improve the health of treated areas [1]. The recent discovery of the mechanically activated ion channels Piezo1 and Piezo2 advanced our understanding of the detection and effects of mechanical signals in cells and the sense of touch [2]. Using vibration to mimic the touch of the skin while simultaneously stimulating Piezo-mediated molecular signaling in underlying tissues could positively affect local tissues and brain function.

Losing a body part or not feeling an extremity impacts a person's ability to navigate daily life, environments, and uneven surfaces. Particular mental and physical challenges, especially pain, atrophy, reduced blood flow, and degeneration of skin and nerves in the residual limb, often require long-term treatment. This review describes the functional connections between peripheral vibratory stimulation and the related physiological adaptations in the brain.

2. Mechanosensitive Piezo Channels

While humans have used touch and massage to induce physiological and psychological effects for centuries, the underlying mechanically sensitive receptors were identified

only recently. Only a thorough understanding of how and when these receptors are active can facilitate the development of technological and therapeutic approaches that target the related cellular and neural mechanisms.

Ardem Patapoutian's lab identified the mechanosensitive nonselective ion channels Piezo1 and Piezo2 [2] that lie on the human chromosomes 16 and 18 [3]. Each channel is a triple-bladed propeller trimer assembled from three Piezo monomers with each blade curved upward and away from the plane of the plasma membrane in a convex arrangement [4–10]. The central pore formed by the three blades opens upon mechanical stimuli including shear stress, compression, pressure, membrane stretching [11–13], whole-cell poking [14], fluid flow [15], pulling [16], and ultrasonic shock waves [17], but also intracellular traction forces [18], chemical agents [19,20], and ionization [21–23]. Extracellular monovalent ions and most divalent ions permeate the nonselective cation channels at negative membrane potentials [24]. While the inactivation time of Piezo1 is ~50% slower than that of Piezo2 [2,25], both channels sense mechanical forces in milliseconds and transduce this information through cation permeability into electrical and chemical signals [26–28]. Such Piezo-pathways trigger Ca^{2+} influx to cells and initiate signaling cascades related to tissue development, homeostasis, and regeneration [18,29].

Piezo1 is primarily found in smooth muscle cells and endothelial cells, while Piezo2 is dominant in mechanosensory neurons [12]. They play essential roles in touch [12], mechanically induced pain [30,31], vascular development [32], blood pressure control [33], nitric oxygen (NO) signaling [34], exercise performance [35], lymphatic valve development [36,37], heart valve development [38,39], formation of new blood vessels [40], neuronal stem cell lineage [41], stem cell differentiation [42], bone formation [43,44], cell migration [18], axon regeneration [45], inflammation [46], red blood cell volume regulation [47], and epithelial cell division and crowding [48,49]. Their coexpression in sensory neurons of the petrosal ganglion and the vagus nerve nodose ganglion, which innervate the carotid sinus and aortic walls, associates both Piezo channels with blood pressure control [33]. However, their exact location in the arterial wall nerve terminals and their involvement in nerve viability has yet to be determined to clarify their role in the baroreflex [27].

The mechanosensitive dorsal root ganglions (DRGs) are clusters of cell bodies of the pseudo-unipolar first-order sensory neurons that transmit touch, proprioception, nociception, and thermosensation [14]. Their expression of Piezo ion channels depends on neuron size. While Piezo2 was expressed in ~90% of all mouse DRG neurons and with a higher expression index than Piezo1, most of Piezo1 was selectively expressed in small-size mouse DRG neurons. In addition, the trigeminal ganglion expresses Piezo2 in neurons transmitting touch. Together with the sensory neurons of the DRG and neurons innervating somatic and visceral structures, they communicate with the jugular and nodose ganglia [10,50,51].

This association of Piezo1 with smaller fibers places Piezo1 in context with the sensation of noxious mechanical stimuli, whereas Piezo2 is most relevant in light-touch and the sense of body position as a part of proprioception [52–54]. Consequently, Piezo1 may be a polymodal sensor for diverse mechanical force detection in the body, while Piezo2 could be tuned to proprioception [13]. While both channels enable touch and body position receptors to detect rhythmic mechanical stimuli in the frequency range 20–100 Hz (Figure 1) [34,51,55,56], focal vibration amplitude and force determine the reflex response which also depends on muscle state, i.e., relaxed vs. active (Figure 2) [57].

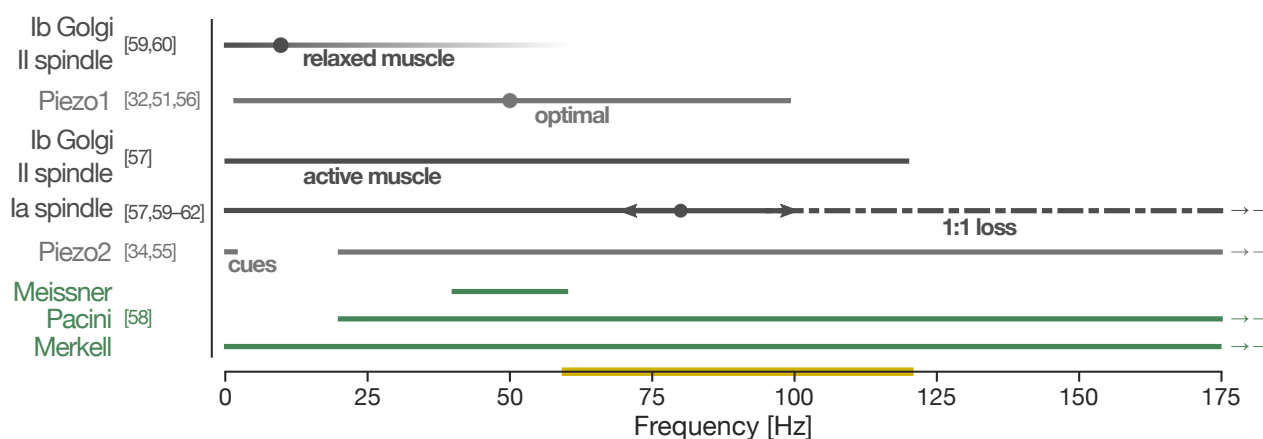


Figure 1. Frequency encoding of mechanosensitive receptors. Colors: recommended range for focal muscle and tendon vibration and vibrotactile feedback—dark yellow on axis; touch—green [58], proprioception—black [57,59–62], and Piezos—gray [32,34,51,55,56].

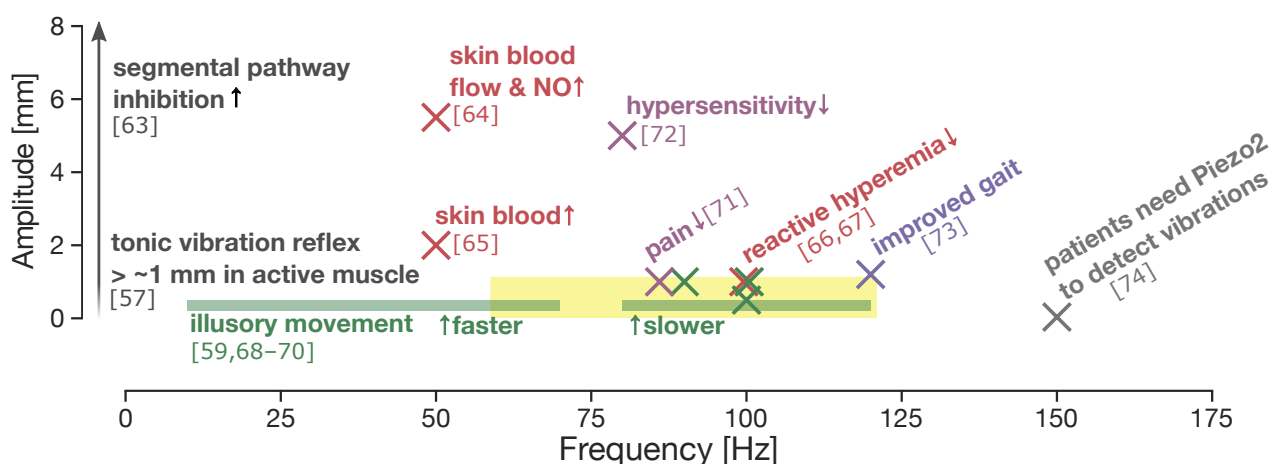


Figure 2. Physiological responses to focal vibration amplitude and frequency. Illusory movement speed induced by increasing tendon vibration frequency is either perceived as becoming faster at frequencies < 70 Hz or as slower at > 80 Hz [59]. Note that the tonic vibration reflex occurs independently of frequency [57,63]. Colors: recommended range for focal muscle and tendon vibration and vibrotactile feedback—dark yellow in background; studies on the vascular system are marked in red [64–67]; sensory feedback and touch—green [59,68–70]; pain—light purple [71,72]; gait—dark purple [73]; proprioception—black [57,63]; and Piezo2—gray [74]. NO: nitric oxygen; ↑: increase; ↓: reduction.

2.1. Piezo1

Piezo1 is expressed in the skin, endothelial cells, arterial smooth muscle cells, blood vessels, red blood cells, tendons, several organs, and in a relatively low amount in DRGs and other ganglia [2,12,32,75–81]. In the skin, Piezo1 could enable mechanotransduction in keratinocytes [82,83], that make up ~95% of the epidermis [84]. The strong expression of Piezo1 in resistance arteries, including capillaries, highlights its pressure and flow-sensing involvement in structural remodeling [15]. Table 1 provides an overview of Piezo1 location, activation, and function, which are essential for the local response to focal vibration therapy.

Table 1. Selected Piezo1 locations, activation mechanisms, and functions which are essential for the local response to focal vibration therapy.

Location [2,12,15,32,75–83]	Activation [2,17–23,28,32,40,85–90]	Function [15,18,28,32–36,40,41,48,51,80,86,91–110]
• skin • keratinocytes • blood vessels • resistance arteries • capillaries • endothelial cells • arterial smooth muscle cells • red blood cells • tendons • lungs • kidney • bladder • colon • relatively low amount in dorsal root ganglion	• shear flow • laminar and turbulent blood flow • cell indentation • membrane stretching • tensile cellular forces of nonmuscle myosin II • sinusoidal vibration 1–100 Hz • substrate displacement • osmotic stress • ultrasound waves • electricity • ionizing radiation • magnetic energy • bioactive lipid mediator sphingosine 1 phosphate (S1P) • chemical agent Yoda1 • chemical agent Jedi2	• nitric oxygen signaling • blood pressure regulation • pressure and flow sensing • vascular tone regulation • endothelial cell alignment to blood flow • angiogenesis • blood vessels formation during development • formation of endothelial tubes in adult tissues • arterial, lymphatic, and venous valve development • vascular smooth muscle remodeling • structural remodeling • stem cell differentiation • stem cell regulation in skeletal muscle regeneration • red blood cell volume homeostasis • cell migration • wound healing • inflammation • arterial remodeling after injury • immune cell function • cell homeostasis • cell fate • protein synthesis, secretion, proliferation, and apoptosis • epithelial homeostasis • tendon compliance • cartilage mechanics • baroreflex • exercise pressor reflex • responses to physical exercise • vasoconstriction of the intestine • vasodilatation of skeletal muscle • bladder mechanosensing • cancer metastasis • neuroprotective and neurotherapeutic effects

2.1.1. Activation

When reversibly flattened into the membrane plane [7], Piezo1 is activated at membrane tensions in the range of 1–5 mN/m [111]. It senses “outside-in” and “inside-out” mechanical forces, including cell indentation [2], shear flow [32,86], membrane stretching [2,89], substrate displacement [90], osmotic stress [85], and ultrasound waves [17,88], but also electricity [21], ionizing radiation [22], and magnetic energy [23]. The bioactive lipid mediator sphingosine 1 phosphate (S1P) activates Piezo1 as well [40]. Chemical activation of Piezo1 is possible with agents Yoda1 [19] and Jedi2 [20], which can be antagonized by Dooku1 [112], and modulated with OB1 [113]. Ensembles of more than ~25 Piezo1 trimers are required to faithfully transduce signals between 1–100 Hz, which enables the robust detection of pulse waves in the physiological range of human heartbeat [51].

There is also ongoing Piezo1 Ca^{2+} signaling through tensile forces created by nonmuscle myosin II activation in the cell’s actin cytoskeleton [114]. These Ca^{2+} flickers regulate ongoing cell signaling and function, affecting cell migration, wound healing, cancer metastasis, immune function, and cell fate [18,92]. Figure 1 shows at which frequencies Piezo1, Piezo2, and other mechanically sensitive receptors discussed in Section 3 can encode mechanical stimuli to chemical and electrical signals.

2.1.2. Function

Piezo1 senses shear stress upon increased local blood flow and membrane stretch upon elevated blood pressure [28]. Piezo1 is important for endothelial cell alignment to blood flow, formation of blood vessels during development [32,86], formation of endothelial tubes in adult tissues [40], stem cell differentiation [41,104], stem cell regulation in skeletal muscle regeneration [102], vascular smooth muscle remodeling [15], arterial remodeling after injury [100], regulation of vascular tone and baroreflex [15,28,34], adaptive changes in blood pressure in response to exercise [35], tendon compliance [80], blood pressure and NO regulation [33,34], red blood cell volume homeostasis [109], epithelial homeostasis [48],

arterial, lymphatic, and venous valve development [28,36,105], cell migration [95,98,106], bladder mechanosensation [93], cartilage mechanics [101,108], and protein synthesis, secretion, proliferation, and apoptosis [94,103]. Thereby, the effect of Piezo1 signaling depends on the structural environment and on the particular context of its activation [115].

The signal cascades upon Piezo1 activation differ for laminar and turbulent blood flow [87]. Its activation not only triggers influx of extracellular Ca^{2+} , but also promotes Ca^{2+} release from the endoplasmic reticulum [111,116,117]. Laminar flow applied to human umbilical arterial endothelial cells leads to ATP production, downstream phosphorylation of AKT (protein kinase B), endothelial nitric oxide synthase (eNOS), and subsequent NO production [34]. However, turbulent flow leads to an inflammatory response through focal adhesion kinase [107]. In inflamed tissues, Piezo1 senses changes in local mechanical stress and participates in the development of the inflammation [99]. Its signaling pathways release destructive mechanical forces and clear the inflammatory necrosis to restore cell homeostasis [103].

Endothelial Piezo1 activated by high blood flow is essential in the whole-body response to physical exercise [91]. Sympathetic activation regulates the autonomic exercise pressor and baroreflex systems to increase systolic blood pressure through vasoconstriction of the intestine. At the same time, vasodilatation of skeletal muscle ensures the delivery of oxygen and nutrition to the muscles [35,97,110]. Subsequently, cardiac output increases, and blood volume shifts towards the periphery [118,119]. Diastolic blood pressure remains primarily unchanged in healthy individuals. Still, it depends on the level of vasodilatation in skeletal muscles [120,121], which is mediated by factors including adenosine, K^+ , histamine, and prostaglandins, NO, as well as levels of pH, O_2 , and CO_2 [122,123].

Piezo1 senses increased blood flow and shear forces and its signaling cascades work in concert with metabolic factors supporting angiogenesis in exercised muscles [124]. Its related NO signaling has additional neuroprotective (before injury) and neurotherapeutic (after injury) effects through the release of brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF) [96].

2.2. Piezo2

Piezo2 is expressed in all known low-threshold mechanoreceptors (LTMRs). It is found in the hairy skin, hairless skin, endothelium, Merkel cells, Meissner corpuscle axons, muscle spindles, Golgi tendon organs, vagal sensory neurons of the lung, bladder, urothelial cells, colon, and kidney, and in relatively high amount in DRGs and other ganglia [2,12,32,55,86,125–131]. While its expression in A δ LTMRs and C LTMRs links Piezo2 to selected types of nociceptors, thermosensation does not require Piezo2 [10]. Table 2 provides an overview of Piezo2 location, activation, and functions which are essential for the systemic response to focal vibration therapy.

Table 2. Selected Piezo2 locations, activation mechanisms, and functions which are essential for the systemic response to focal vibration therapy.

Location [2,10,12,32,55,86,125–131]	Activation [10,12,31,32,34,50,51,55,132]	Function [10,12,13,31,33,54,55,74,130,133–136]
• hairy and hairless skin • low threshold mechanosensitive receptors • vagal sensory neurons • Merkel cells • Meissner corpuscle axons • muscle spindles • Golgi tendon organs • endothelium • lungs, kidney, colon • bladder and urothelial cells • relatively high amount in dorsal root ganglia and other ganglia	• touch • gentle brush • vibrations > 20 Hz • vibration onsets < 2 Hz • itch • tactile allodynia • blood flow and pressure • breathing • bladder stretch • digestion • interoceptive processes	• mechanosensation • detect vibration • detect joint movement direction • light innocuous touch detection under normal & inflammatory conditions • balance • gait stability • coordination • proprioception • reflex regulation of breathing • respiratory tidal volume regulation • hearing • endothelium-dependent pain • tumor angiogenesis

2.2.1. Activation

Piezo2 is activated during light touch, reflex regulation of breathing, bladder control, digestion, blood pressure regulation, several interoceptive processes, hearing, and itch [10,12,55]. It is necessary for detecting gentle brush and vibration [31,32,34,55,132], but not for sensing deep pressure [137]. In mice, Piezo2 is required for transducing constant vibrations > 20 Hz as well as for detecting vibration onsets < 2 Hz (Figure 1) [32,34,51,55]. In patients, Piezo2 was not involved in transmitting ordinary mechanical pain [31,138]. However, Piezo2 plays a role in tactile allodynia, a pathophysiological pain sensation elicited by only touching or brushing affected skin [50].

2.2.2. Function

Piezo2 is essential for human mechanosensation, i.e., the sensation of light touch under normal and inflammatory conditions [31], and is involved in endothelium-dependent pain and tumor angiogenesis [134,136].

Conditional Piezo2 knockout almost abolished ion currents of rapidly adapting LTMRs in adult mice, which caused severe deficits in gait stability and the sensation of innocuous touch [55]. While Piezo2 knockout in neurons specific to proprioception led to severely impaired limb coordination, knockout in proprioceptive neurons of the mesencephalic trigeminal nucleus led to impairments in coordination and balance [13,54,130,133]. In adult Piezo1/2 conditional double knockout mice, the absence of Piezos in visceral vagus nerve nodose sensory ganglion neurons impaired the lung Hering–Breuer reflex and increased the respiratory tidal volume [33,135]. These findings highlight the role of Piezo2 in proprioception, the autonomous control of breathing, motor control, and locomotion.

In two patients with Piezo2 deficiency syndrome, Piezo2 was required to detect vibration at 150 Hz with 17 μ m amplitude (Figure 2, correct detection of patients vs. control; mean $\pm$ standard deviation: $40 \pm 14\%$ vs. $98 \pm 0.5\%$, respectively), general touch only of hairless skin (4.2 ± 0.7 g vs. 2.9 ± 0.2 g, respectively), and the direction of joint movement ($50 \pm 10\%$ vs. 100% , respectively) [74]. Similar to healthy participants, these two patients detected non-noxious deep tissue pressure already at 30 mmHg, whereas A β -deafferented patients could not, suggesting a not-yet-known sensor for non-noxious deep pressure [137].

2.3. TRPs and Other Mechanosensitive Channels

Transient receptor potentials (TRPs) have an overlapping function with Piezo ion channels. However, only specific neuron populations that do not overlap with those expressing Piezo1 express TRPV1 [52]. TRPs are located in many body systems, including

the brain, DRG, trigeminal ganglion, vagal ganglion [139], perivascular sensory neurons, keratinocytes, immune system, smooth muscle cells, and bladder [140]. Physical and chemical stimuli can trigger TRPV1 activation, causing membrane depolarization and Ca^{2+} influx that leads to diverse responses, including smooth muscle contraction, neuronal excitation, and secretion [141]. However, the direct mechanical activation of TRP channels was only proven in *Drosophila melanogaster* flies [101,142,143]. However, there are other directly mechanosensitive sensors besides Piezos [85], e.g., MscL [144,145], MscS [145], TRAAK [146], TREK-1 [146], and several OSCA family members [147], that are beyond the scope of this review.

Similar to Piezo1, TRPV1 activation leads to phosphorylation of protein kinase A and eNOS [148], which causes relaxation of vascular smooth muscle cells via NO- and K^{+} -dependent pathways [141,149,150]. In addition, its eNOS- and Ca^{2+} -dependent PI3K/AKT pathway protects the endothelium [141].

TRPs are involved in multiple processes, including pain [151], thermosensation (TRPV1 $> 43^{\circ}\text{C}$, TRPM8 cold) [152,153], low extracellular pH [153], axon survival (TRPV4) [154], stem cell fibrillar collagen assembly [29], blood pressure regulation [155], energy homeostasis [156], modulation of autophagy and proteasome activity [157], reciprocal crosstalk between the sensory nervous and immune systems [158], regulation of diet-induced obesity, insulin and leptin resistance [159], cancer [160,161], the development of severe bronchial asthma [162], and even in itch and inflammation [163].

3. Sense of Touch

While the body's largest organ, the skin, protects from external factors, its interaction with the environment is essential for creating the body image and perception. Understanding the mechanisms of the detection of touch and the subsequent signal processing allows us to identify and fine-tune therapeutic strategies that target specific areas of application, such as phantom sensations in people with amputations.

Most low-threshold mechanoreceptors (LTMRs) can transduce dynamic forces greater than 0.5 mN from skin stroke, indentation, and vibration [164–170] to the primary and secondary sensory cortices [58,171,172]. The classification of LTMR fibers distinguishes between fast-conducting (~ 15 – 100 m/s), thickly myelinated, slowly adapting (SA) A β fibers (A β SA-LTMRs); fast-conducting, thickly myelinated, rapidly adapting (RA) A β fibers (A β RA-LTMRs); medium-conducting (~ 5 – 30 m/s), thinly myelinated A δ fibers (A δ LTMRs); and slow-conducting (~ 0.2 – 2 m/s), unmyelinated C fibers (C LTMRs) [58,173–178].

The outer layer of the skin consists of dead keratinocyte cells. C LTMRs nerve endings terminate in the second layer of the skin [82] which mainly contains functional keratinocytes that are nourished via osmosis from deeper layers [84]. The next deeper and thicker layer is the dermis, which connects to A β and A δ LTMRs and has direct blood supply through superficial blood capillaries [179]. Below the dermis, larger nerves and blood vessels supply subcutaneous tissues, muscles, and bones. The subsequent pathway of the transmission of sensory information involves first-order neurons, the DRG, the dorsal horn, and the spinal cord. Then the sensory information crosses the midline in second-order neurons in the dorsal column nuclei, where the *formatio reticularis* lies, and travels via third-order neurons from the thalamus to the somatosensory cortices [173]. While attention plays almost no role in transferring the signal through this pathway [96,180], interneurons [91,181,182] and the ascending reticular activating system may modulate the signal along the way [183].

Hairless skin has four types of tactile sensors: Meissner, Ruffini, and Pacinian corpuscles, as well as Merkel cell–neurite complexes [179,184–186]. However, histologic preparations rarely found fibers of Ruffini corpuscles [187]. LTMRs are associated with first-order mechanosensory neurons that have their cell bodies in the DRG and sensory ganglia of the cranial nerves [188]. The classification of LTMR fibers orders them by decreasing myelin sheath thickness as A β , A δ , or C [179,188]. This notation is combined with a functional classification in subtype 1 or subtype 2 of rapidly adapting (RA) or slowly adapting (SA) fibers (see conduction velocities in Section 2.2) [189,190]. Subtype 1 has a

smaller receptive field area than type 2 [191]. Morphologically, the Meissner corpuscle connects with RA1 (receptive field area range: 9–636 mm²), the Pacinian corpuscle with RA2 (39–5223 mm²), the Merkel cell–neurite complex with SA1 (5–29.5 mm²), and the dermal Ruffini corpuscles with SA2 (7–1346 mm²) [184,187,191].

Hairy skin has Pacinian corpuscles, Merkel cell–neurite complexes, Ruffini corpuscles, and C-tactile mechanoreceptive afferents [192–194]. The degree of tactile feedback varies for each LTMR type [173]. In mice, Piezo2 plays an essential role in mediating air-puff, vibration, and brush responses across nearly all molecularly distinct classes of A β LTMRs [2,31,58,74,127,128,132,195] and A δ LTMRs, but is less involved in C LTMRs [30].

Subepidermal Schwann cells surround peripheral nerves and are essential for axon viability but may also transduce mechanical stimuli to sensory nerve endings, mediating the sensations of touch and pain [127,196,197]. They rely on the tether-like protein USH2A to maintain the local stiffness required for the mechanical activation of Piezo2 [30,55,90,113,198].

Keratinocytes make up 95% of the epidermis [84] and express high levels of mechanosensitive Piezo1 [2] and several thermosensitive TRP channels, including TRPV1, TRPV4, TRPV3, and TRPM8 [83,199–204]. Piezo1 is a likely, but probably not the only, candidate that enables mechanotransduction in keratinocytes [82,87,205].

Human and primate Meissner corpuscle (A β RA1-LTMR) lie below the epidermis [187,206]. They are especially sensitive to frequencies between 40–60 Hz [58] and to discriminative gentle touch [206] (Figure 1). In patients with multiple sclerosis, POEMS syndrome (peripheral neuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes), and Charcot–Marie–Tooth disease, reduced numbers of Meissner corpuscles were reported [187].

Pacinian corpuscles (A β RA2-LTMR) are located deep in the skin [206] and detect skin deformations as little as 30 nm [58]. Surrounded by Schwann cells that shield them from lower frequencies [58,207], Pacinian corpuscles sense light forces delivered between 20–1500 Hz and are especially sensitive to vibrations between 200–400 Hz, as well as to deep pressure [189,190,208–211]. Since Piezo2 loss-of-function mutations in humans and deletion of Piezo2 in mice lead to insensitivity to 150 Hz vibration, Piezo2 may be responsible for mechanotransduction in Pacinian corpuscles [31,74,132], but not for their deep-pressure-sensing capabilities [137] (Figures 2 and 3). However, the exact location of Piezo2 in Pacinian corpuscles is not yet known [207].

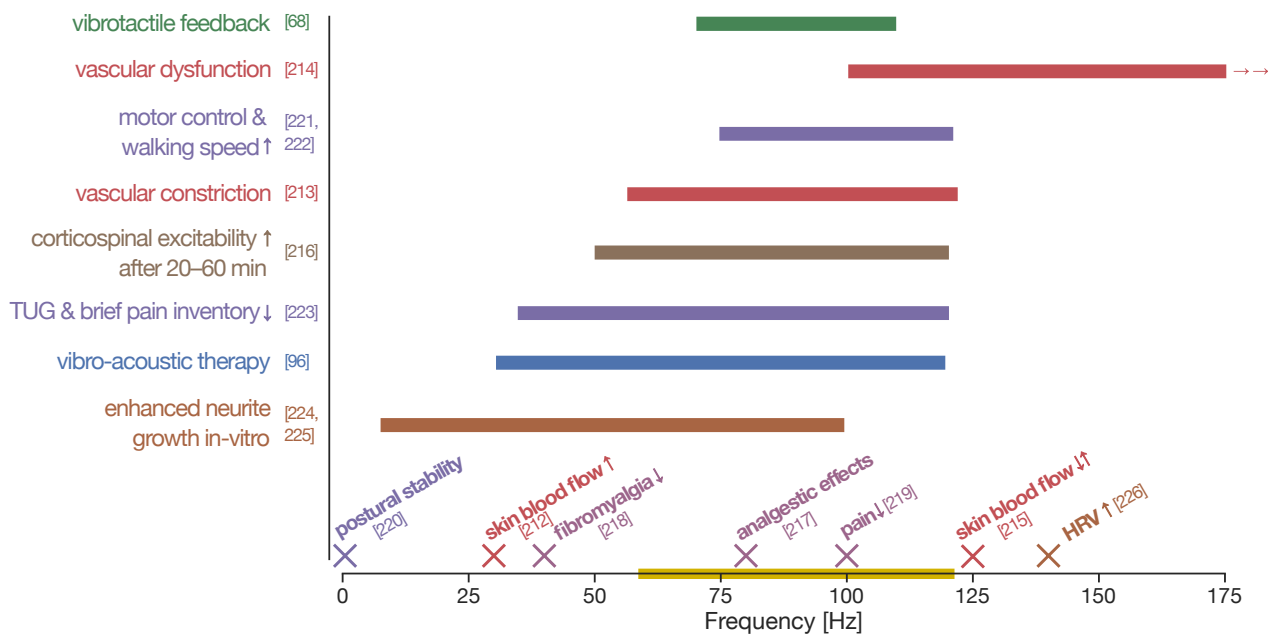


Figure 3. Physiological response to various focal vibration frequencies. Colors: recommended range for focal muscle and tendon vibration and vibrotactile feedback—dark yellow on axis; studies on the vascular system are marked in red [212–215]; sensory feedback and touch—green [68]; corticospinal excitability—brown [216]; focal muscle vibration range—blue [96]; pain—light purple [217–219]; locomotion—dark purple [220–223]; central nervous system—orange [224–226]. HRV: heart rate variability; TUG: timed up & go; ↑: increase; ↓: reduction.

Merkel cell–neurite complexes (A β SA1-LTMR) are located at the boundary between dermis and epidermis and form the touch-domes of the hairy skin [58]. They are sensitive to touch and pressure for up to 30 min, aid in two-point discrimination, and can generate action potentials up to frequencies of 300 Hz (Figure 1) [58,82,208,209]. They also rely on the tether-like protein USH2A [198] and express Piezo2 [127,129].

Ruffini corpuscles (A β SA2-LTMR) lie in the reticular layer of the dermis and within joints [227]. In the human skin, their density is <0.3 corpuscles/mm², where they sense stretching of the skin around objects and over joints [208,209]. While neurophysiological recordings identified neurons with properties corresponding to A β SA2-LTMR [228], morphological analysis often did not find Ruffini corpuscles within the expected regions of the skin [229]. Thus, the association between A β SA2-LTMR and their potential end organ(s) remains unclear [58].

Touch, Proprioception, Pain, and Gate Control

After LTMRs detect sensory cues in the periphery, the brain and spinal cord modulate these signals, i.e., the pathways of touch and pain are not independent. The neural circuitry in the dorsal horn allows the sensations of touch and pain and several central inputs to affect each other. In addition, human touch and pain signaling pathways are complementary through nociceptors with pathways similar to touch afferents. While A β fibers exclusively signal aspects of touch, A δ and C fibers signal pain in addition to temperature and gentle touch (Figure 4) [138,230–234].

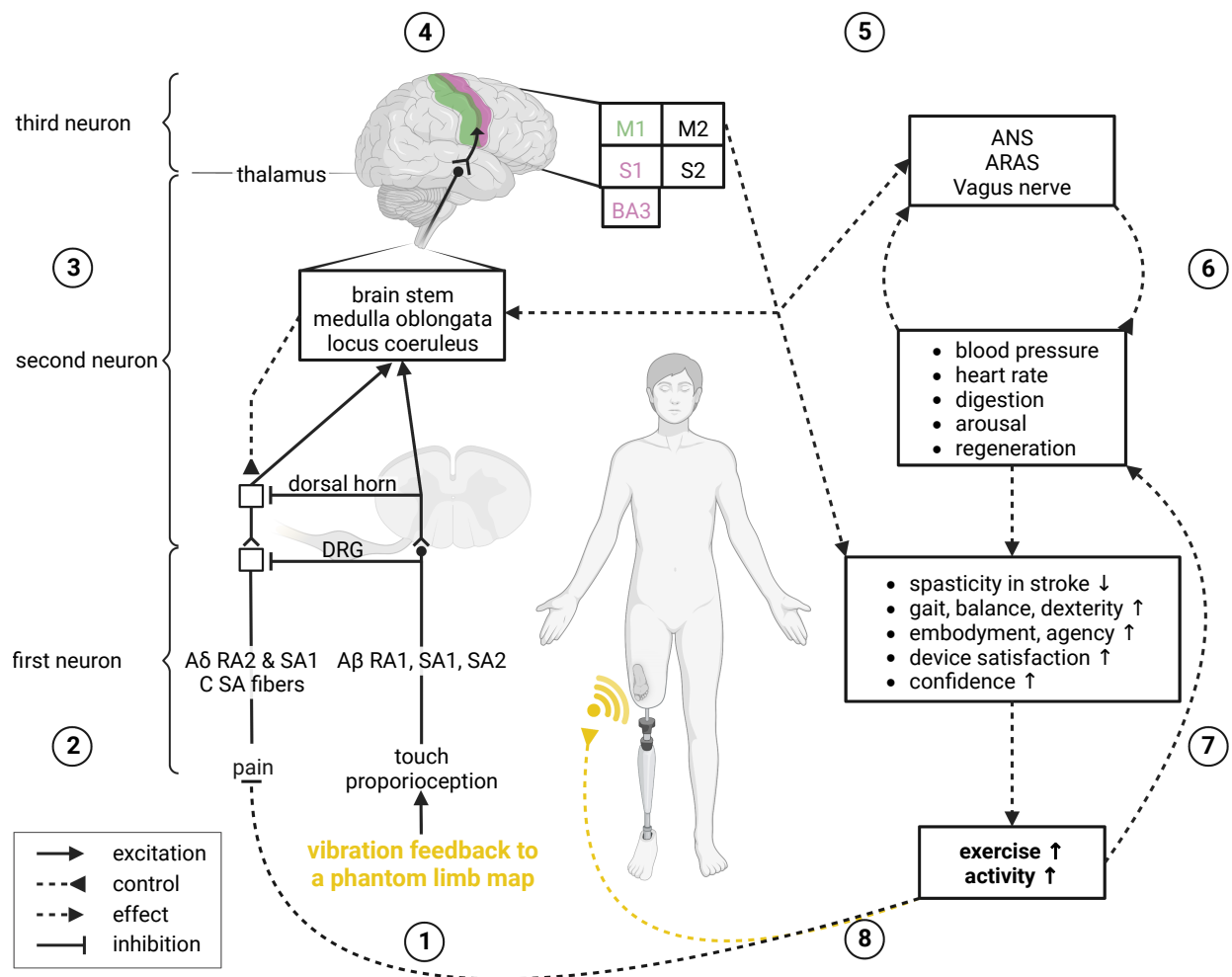


Figure 4. General neuromodulation pathways of vibratory feedback. (1) Focal vibration stimulates an area that a person associates with a denervated limb [235]; (2) afferent signals of touch and proprioception travel through first-order neurons to the DRG [14], where they can inhibit pain already

in the peripheral nervous system [236]; (3) while the circuitry of the dorsal horn allows touch and central inputs to modulate pain [52,237], the signals travel through the medulla oblongata and the locus coeruleus in the brain stem to the somatosensory and motor cortex areas (4) and interact with the ANS, ARAS, and vagus nerve along the way (5) [183,238,239]; (6) the stimulated ANS controls several body functions, and processes inputs from the periphery, e.g., during exercise and activity [35,240–242]; (7) recovery of the somatosensory and motor areas improves motor control through neurological and psychological mechanisms, thus prompting a more active lifestyle [243–245] that in turn (8) generates beneficial afferent sensory inputs directly and through related vibrotactile feedback that may inhibit pain. **ANS:** autonomic nervous system; **ARAS:** ascending reticular activating system; **BA:** Brodmann area; **DRG:** dorsal root ganglion; **M1 | M2:** primary | secondary motor area; **RA | SA:** rapidly | slowly adapting receptor; **S1 | S2:** primary | secondary somatosensory area; ↑: increase; ↓: reduction.

For example, while adult Piezo2 conditional knockout mice lack the sensation of gentle touch, they still perceive painful stimuli [31]. Piezo2 was associated with allodynia and hyperalgesia in neuropathic pain [50,83,246] and may be involved in pathologic sensitization of peripheral and central pain pathways and the disinhibition of central pain-dampening circuits [83]. Additionally, the coexpression of Piezo1 and TRPV1 in the DRG and the trigeminal ganglia suggests TRPV1-mediated roles of Piezo1 in pain [52,53].

In the dorsal horn, the excitatory and inhibitory interneurons and projection neurons create a microcircuitry that allows tactile inputs and the descending drive to influence the sensations of temperature and pain [82,173]. The gate control theory of pain of Melzack and Wall [181], later becoming part of the more inclusive neuromatrix theory of pain [96,236,237], acknowledges the microcircuitry of the dorsal horn. In the gate control theory of pain, fibers transmitting touch and pain synapse in distinct regions of the dorsal horn, i.e., the substantia gelatinosa and the transmission cells. Their circuitry allows descending (central) fibers to modulate the interplay of large fibers closing the gate (inhibitory, faster, proprioception) and small C fibers opening the gate (excitatory, slower, nociception) [237]. For example, vibration activates more A LTMRs than C LTMRs and should close the gate. Another essential point of this theory is that the central nervous system creates the sensation of pain, though central and peripheral inputs strongly modulate this process.

Thereby, the signal intensity should also affect the process when inputs from larger fibers sum with the pain signals at the transmission cells. For example, an adenosine-related analgesic effect was found with 80 Hz vibration (2.5–3.5 s trains every 20–25 s for 10 min in cats) which depressed lower lumbar nociceptive neurons for up to 4 h [96,217]. In addition, 80 Hz, 0.5 mm, 1 N muscle tendon vibration reduced pain intensity by >30% by predominantly activating muscle spindle RA Ia afferents, and additionally activating cutaneous receptors even reduced pain intensity to 51% [247,248]. Consequently, sensory inputs from muscle spindles also modulate pain. Figure 3 shows several local and systemic responses of focal vibration to frequency.

Further observational results showed that the effects of adenosine-modulated vibration reduced low-intensity but enhanced high-intensity pain and itch [181,249–251]. In people with complex regional pain syndrome that is related to impaired central processing of proprioceptive information [252], 86 Hz, 1 mm vibration applied for 20 min a day, five days a week, for ten weeks reduced pain, and improved range of motion (Figure 2) [71]. In rat hind paws immobilized for eight weeks, 80 Hz, 5 mm vibration inhibited the development of paw hypersensitivity and central sensitization when vibration started immediately after the immobilization but not when starting four weeks later (Figure 2) [72]. In addition, people with amputations use this mechanism to reduce phantom limb pain by gently tapping the stump [253], whereas higher pressure may increase the pain [254].

Thus, touch therapy should be considered a complementary method to treat pain and depression and has implications in neonatology, pediatrics, oncology, and geriatrics [1]. For example, non-noxious sensory stimulation of C LTMRs during touch therapy activates areas in the limbic system, the locus coeruleus, and raphe neurons [255]. Such social touch triggers the release of oxytocin from neurons in the hypothalamus that stimulates prosocial behavior, reduces psychological stress, increases emotional wellbeing, and has analgesic, anti-inflammatory, and regenerative effects on the human body [256].

4. Focal Vibration Therapy

Vibration applied focally/locally to peripheral tissues such as muscles or tendons is distinguished from pharmacology, psychotherapy, and physical therapy interventions [242]. Its effect depends on the anatomical location, physical properties, and spatiotemporal parameters. On the one hand, focal vibration therapy affects the central nervous system through neurostimulation, which is termed neuromodulation [182]. On the other hand, it affects local tissues such as blood and lymphatic vessels. Figures 1 and 3, this section and the next, provide an overview on the application of several vibration parameters in focal vibration therapy. To guide the selection of vibration parameter values for specific applications Figure 2 provides an overview of physiological responses to focal vibration amplitude and frequency.

Together with the stimulation duration and composition of the stimulated area, the chosen vibration amplitude, frequency, and rarely reported force or acceleration parameter values determine the receptor response and the effects on the body. For example, higher vibration frequencies increase the mechanical stress and strain on artery walls, either directly

or through increased flow-mediated shear stress [214,257,258]. Focal vibration between 60–125 Hz induced α 2-adrenergic receptor-mediated vasoconstriction of skin blood vessels [213,259,260], and vibration at 125 Hz reduced finger blood flow through increased vascular resistance. However, this was followed by temporary vasodilation after each vibration exposure when compared with values of control fingers (Figure 3) [215]. Thus, an intermittent vibration mode is essential to achieve vasoprotective effects.

Mostly independently of frequency [57], focal vibration of muscles or their tendons can trigger involuntary contractions at tendon vibration amplitudes between 0.3–1.8 mm [61,63,261]. The response to the vibration can be voluntarily suppressed [61] and depends on the chosen muscle, the stimulation site (muscle tendon vs. belly), muscle length, visual inputs (open vs. closed eyes) [216,261], muscle state (relaxed vs. active) [57], contraction/vibration history [262], and the chosen stimulation parameters amplitude, acceleration, and frequency. The activation of muscle spindles mediates the tonic vibration reflex and Golgi tendon organ afferents through monosynaptic and polysynaptic reflexes, including the reciprocal inhibition of the antagonist muscle and descending inputs [216]. In addition, post-activation depression with prolonged activation of Ia afferents reduced motoneuron excitability [247,263,264]; however, preconditioning a muscle with vibrations at shorter lengths facilitated the tonic vibration reflex at subsequent longer lengths [262]. Thereby, the inhibitory input of Golgi tendon organ SA Ib fibers may be most potent at frequencies up to 10 Hz, while only a few fibers were responsive up to 50 Hz [60]. In addition, secondary muscle spindle type II fibers were predominantly activated at low tendon vibration frequencies up to 20 Hz, with few active up to 60 Hz (Figure 1) [60]. While type Ia, Ib, and II afferent fibers of active muscles may not encode higher frequencies in a one-to-one manner, they still modulate the segmental reflex pathway at all frequencies [57].

Vibration amplitudes applied to muscle tendons between 0.2–0.5 mm also activated RA Ia spindle afferents [59,60] while avoiding tonic vibration reflex < 0.3 mm [63] as well as muscle fiber injury [265]. However, experiments applying smaller vibration accelerations avoided tonic vibration reflex even up to 1 mm (Figure 2) [57]. Thereby, the range from 70–100 Hz predominantly activated Ia spindle afferents sensing muscle length change with an optimum around 80 Hz [59,60]. Between frequencies from 80–150 Hz, the one-to-one transduction of Ia activation and monosynaptic motor unit response shifts from harmonic to subharmonic transduction and becomes subharmonic > 150 Hz (Figure 1) [60–62]. For example, 50–120 Hz, 1 mm focal vibration of relaxed muscles increased the amplitude of motor-evoked potentials [216], which is related to the excitation of corticospinal pathways that transmit afferent Ia signals to their central representations in the contralateral and the ipsilateral hemisphere [266,267]. In summary, 0.1 mm muscle vibration induced less inhibition of the segmental reflex pathway than 0.3 and 0.5 mm, but already amplitudes > 0.3 mm become more likely to evoke a tonic vibration reflex [63]. Similarly, tendon vibration from 0.2–0.5 mm did not trigger involuntary muscle contractions [60], but started and became stronger from 0.6–1.8 mm [61,261]. However, amplitudes > 0.3 mm could be necessary to overcome the damping effects of subcutaneous tissues for effective muscle stimulation [216]. Focal vibration therapy should consider all these mechanisms.

Figure 5 shows focal muscle or tendon vibration amplitude, frequency, and outcome of 61 vibration intervention groups from 56 studies that were screened by nine systematic reviews [268–276]. The data include 1218 participants with an average age of 43.8 years, ranging between 2–73.7 years [216,266,267,277–329]. The vibration duration in those studies lasted up to 60 min per session, with a mean of 18.7 min. A total of 72.1% of the studies reported mainly positive outcomes, and only one reported an unexpected, but not harmful, result, which was a 5% reduction in voluntary peak torque following 70 Hz and 1.5 mm Achilles tendon vibration [277]. Using vibrotactile feedback in focal vibration therapy targeting pain, motor control, gait, and blood vessels, we identified the highest-density regions that cover $\sim 70\%$ of the used vibration parameters. The resulting frequency values lie between ~ 60 –120 Hz and amplitudes values reach up to 1 mm (Figures 1–5). In the selected

range, the average $\pm$ SD for frequency is 94 ± 16 Hz, and for amplitude, it is 0.5 ± 0.4 mm (Figure 5).

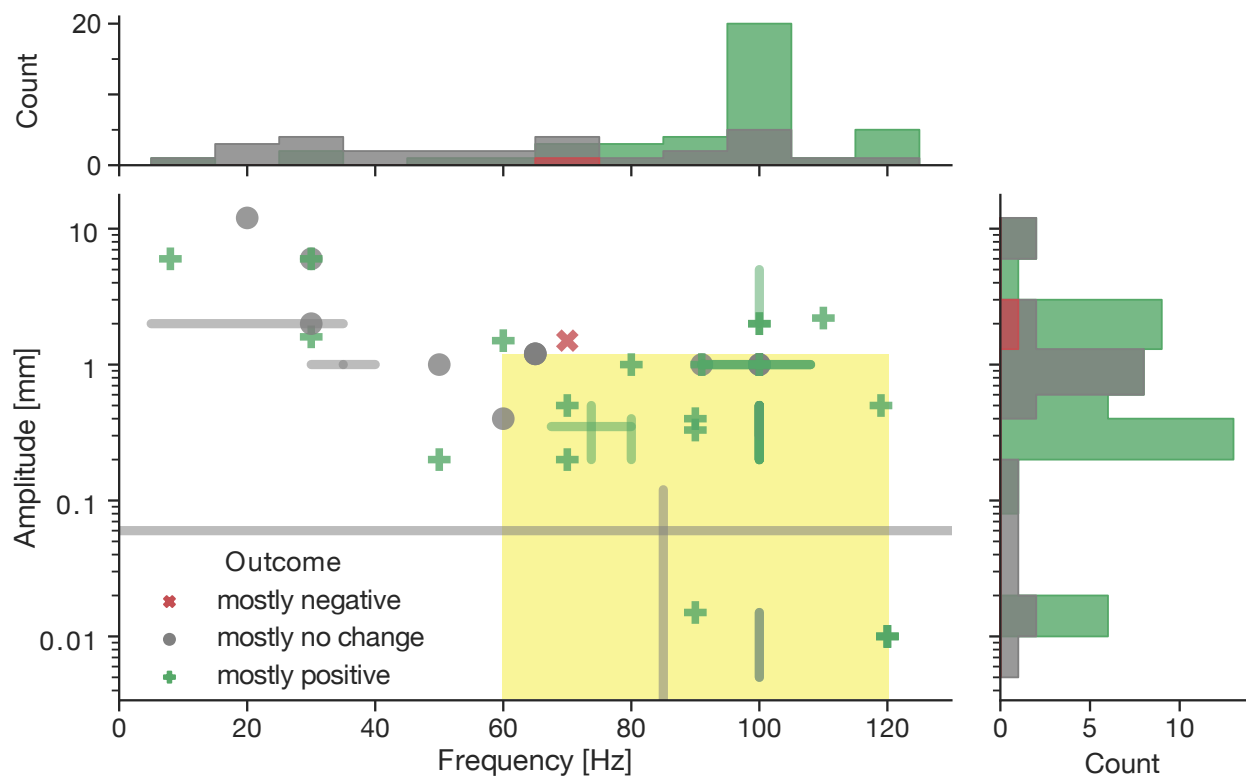


Figure 5. Color-coded scatter plot and histograms of frequencies and amplitudes used in 61 intervention groups from 56 studies on focal muscle or tendon vibration [216,266,267,277–280,282–298,301–324,326–329] that were selected by nine recent systematic reviews [268–276]. Parameter ranges from studies are shown as gray (neutral) and green lines (positive outcome). Four studies using 300 Hz, 2 mm vibration are not shown [281,299,300,325]. Studies listed in the systematic reviews not reporting amplitude were excluded.

Most systematic reviews did not report adverse effects of focal vibration therapy [242,275, 276,330–334]. A total of 73% of the included studies report positive results on performance measures in healthy people [270,272], motor conditioning in healthy people [271], balance in older adults [274], upper extremity spasticity in people with stroke [268,335], gait and postural stability in people with neurological disorders [269], and neurorehabilitation [273] without adverse effects. Only focal dystonia, a movement disorder that causes involuntary muscle contractions, is related to an abnormally increased tonic vibration reflex and may contribute to maladaptive cortical plasticity, altered sensorimotor integration [336–339], and hypersensitivity to vibration [340]. Additionally, the outcome of focal vibration therapy in patients depends on the specifics of the injury or disease, e.g., the extent and location of an ischemic infarct [341].

Only a few studies reported null results, which may be an effect of publishing practices that often favor positive outcomes. For example, while 30 min of 100 Hz Achilles tendon vibration reduced H-reflex amplitude but not peak plantar flexor torque [342], 20 min of 70 Hz reduced peak torque but not voluntary activation [277]. A training intervention with three sets of biceps curls, each up to ten repetitions or until failure, twice a week, and for eight weeks, using superimposed 30 Hz vibration improved elbow flexor one-repetition maximum but not isometric break force [343]. In addition, adding 65 Hz, 1.2 mm superimposed vibration for only one or two minutes to sets of biceps curls and ballistic knee extensions did not affect physical performance [286–288]. Similarly, 30 Hz, 6 mm hamstring vibration did not immediately affect muscle strength and single-leg hop distance [278].

However, in rats, frequencies above 100 Hz increased vascular dysfunction, inducing remodeling, oxidative activity, and inflammation (Figure 3) [214]. In addition, rat hind limbs and tails experienced peripheral nerve degeneration already after five to six days when exposed to 60–82 Hz, 0.21–0.4 mm vibration for two to five hours per day [344, 345]. However, translating such adverse effects from rats, most likely related to vibration amplitude, to humans would require appropriate scaling to body size, which would exceed practices used in focal vibration therapy.

5. Peripheral Effects of Focal Vibration

Depending on vibration amplitude and location, focal vibration penetrates several layers of tissue. While damaged blood vessels are present in various pathological scenarios, including diabetes, amputation, and peripheral neuropathy, Piezo1-mediated signaling pathways may positively affect the tissue quality of the stimulated tissues. This section establishes the connections between intra- and intercellular pathways of mechanically triggered Piezo1 signaling and focal vibration therapy that aim to affect sensory signaling, cell repair, growth, maintenance, and degradation.

Focal vibration stimulates endothelial cells via direct and central mechanisms that induce Ca^{2+} and adrenomedullin-eNOS-NO signaling in blood vessels and lymphatic vessels [28,96,346,347]. It affected vascular smooth muscle [348], increased skin blood flow after vibration [64,212,349], and triggered a combined metabolic, neurogenic, and myogenic response to 10 min of 100 Hz, 1 mm vibration, but no discernible response to 35 Hz or sham control conditions [66]. In diabetic patients, 5 min of 50 Hz, 2 mm intermittent focal vibration applied to the foot sole (two conditions: 10 s on, 5 s off for 7.5 min; or 10 s on, 10 s off for 10 min) increased skin blood flow at the foot sole, while 5 min of continuous vibration did not [65]. This is explained by the effect of intermittent vibration between 30–125 Hz which triggered blood vessel constriction followed by dilatation [64–66,212,215]. Such effects may counteract reactive hyperemia in load-bearing conditions during activities similar to walking (Figures 2 and 3) [67], which supports choosing intermittent over continuous vibration to affect the vascular system.

5.1. Vascular Regeneration

The development and maintenance of the vascular system rely on mechanical cues that trigger situation-dependent adaptations. For example, shear flow or stretch elicit vascular endothelial cell remodeling through Ca^{2+} -mediated pathways that may be optimally triggered around 50 Hz mechanical Piezo1 stimulation [56]. In addition, mechanotransduction-modulated molecular signaling, and changed gene expression profiles can affect the alignment of cytoskeletal structures [350]. In adult cells, the activation of Piezo1 is essential for epithelial cell mass formation [49,111] and endothelial sprouting [40] but is also critical for embryonic vascular development [2,32]. For example, in vitro and in the presence of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF), shear stress stimulation applied to the surfaces of bovine pulmonary microvascular endothelial cells increased microvessel formation by 1.9-fold when compared to no stimulation [351]. In addition, a cyclic stretch of rat cerebral microvessel endothelial cells induced 1.3-fold greater total tube length growth compared to constant static stretch [352].

In gels containing fragments of rat microvessels exposed to VEGF, delayed mechanical stimulation enhanced vascular network formation through a proangiogenic response of the strain gradient sensing gene *Itga2* compared to early stimulation [353]. Thus, the timing, type, and location of Piezo1 stimulation dictate the resulting pathway and its outcome.

Thereby, the extracellular matrix conveys mechanical forces [354,355] related to capillary growth, and vascular remodeling in human primary dermal vascular endothelial cells and mouse embryos are orchestrated via VEGF [356]. Nevertheless, region-specific differences in the extracellular matrix stiffness mediate the growth and formation of adjacent tissues [357,358]. Regions with high Piezo1 activity may drive vascular remodeling [115], and primary cilia in the endothelium convert the sensed fluid shear stress into

Ca^{2+} -dependent signaling pathways [359]. For example, an intermediate stiffness of the extracellular matrix was optimal for VEGF receptor-2 (VEGFR-2) expression that enhanced sprout formation and was correlated with VEGF concentration [356,360,361]. Thereby, VEGF upregulates the expression of eNOS, and the release of NO, a key mediator of angiogenesis [86,362–365] promoting the regeneration of endothelial function [366]. Figure 6 illustrates the effects of activating Piezo1 in the endothelium (of human and mouse cell cultures as well as genetically modified mice) [28].

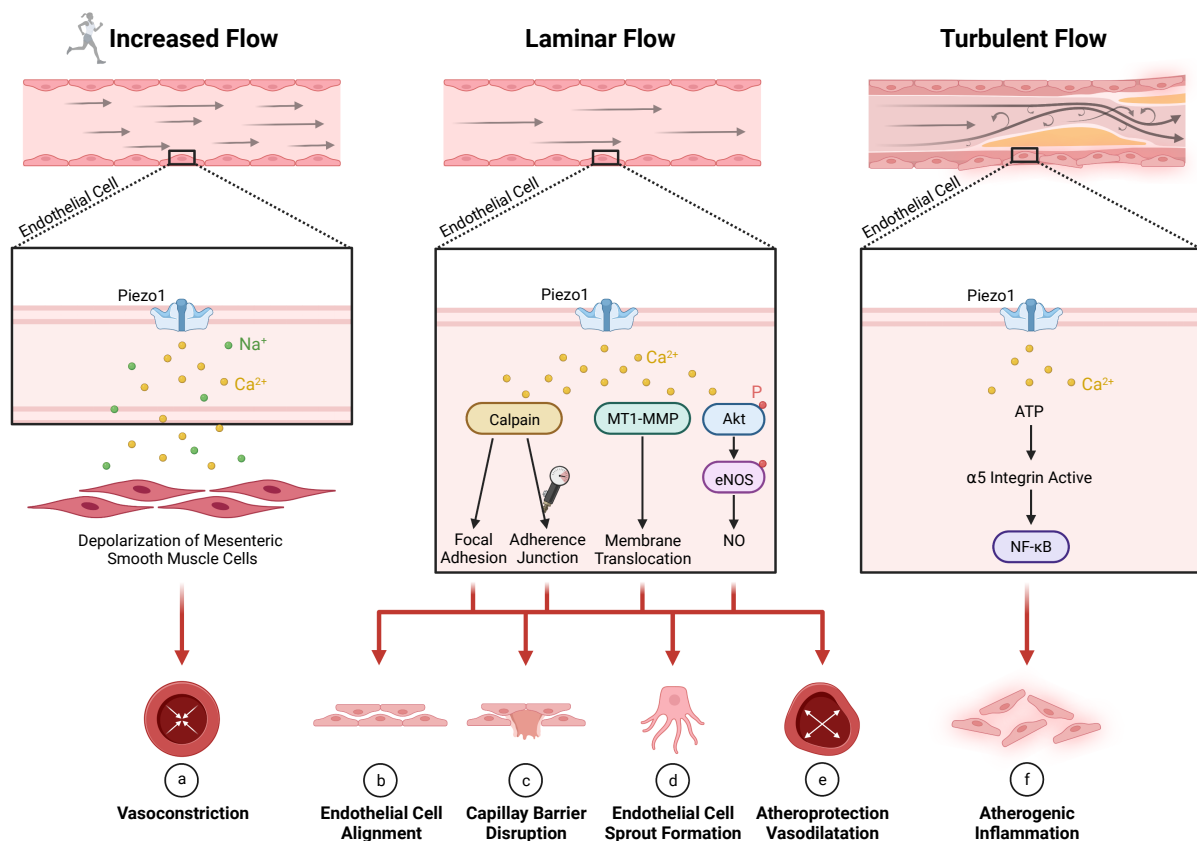


Figure 6. The signaling pathways and outcomes of Piezo1 activation in the endothelium depend on blood flow direction, frequency, and intensity [34,35,40,86,107,367–369].

- (a) High blood flow during physical exercise leads to vasoconstriction through Na^{+} - and Ca^{2+} -induced depolarization of mesenteric artery smooth muscle cells [35], while increased pulsatile laminar shear stress promotes mitochondrial biogenesis and signaling [370];
- (b) Laminar flow shear stress during embryonic development leads to endothelial cell alignment through Ca^{2+} -activated calpain and focal adhesions [32,86,371–375];
- (c) High hydrostatic pressure in lung capillaries leads to endothelial barrier disruption (associated with lung edema) through Ca^{2+} -induced calpain activation [367];
- (d) Laminar flow shear stress or S1P without mechanical stress lead to endothelial cell sprout formation through Ca^{2+} -induced activation, and membrane translocation of membrane type-1 matrix metalloproteinase [40];
- (e) Laminar blood flow leads to atheroprotective vasodilatation in the periphery through phosphorylation of AKT and eNOS synthesizing endothelial NO [32,34,86,112,371, 376–384] which is associated with factors, including VEGF [356], bFGF [368,385,386], microRNAs miR-126 [387,388], and miR-17–92 [369];

- (f) Turbulent flow leads to atherogenesis through the nuclear factor (NF) $\text{NF-}\kappa\text{B}$ [107] and YAP/TAZ pathways (Yes-associated protein/transcriptional coactivator with PDZ-binding motif) [389], and to endothelial cell activation via enhanced glycolysis [370];
- (g) Hypertension in smooth muscle cells of resistance arteries leads to arterial remodeling through stimulation of transglutaminase II (not depicted) [15].

In addition, the presence of noncoding microRNAs (miRs) in plasma and serum affects related physiological processes [390]. miRs affect the expression of their target gene by binding to the 3'-untranslated region of the messenger RNA [391]. For example, several effects of physical exercise are mediated via upregulated miRs, including the regulation of angiogenesis (miR-126), anti-inflammatory agents (miR-126, miR-146a), and tumor suppression (miR-1, miR-133a, miR-206) [392]. While high expression of miR-221 and miR-222 promotes proliferation in cancer cells [393,394], the miR-17-92 cluster in concert with VEGF [369] and miR-126 in response to VEGF and bFGF promote angiogenesis [368,385,386]. Given the direct blood supply of nerves [395], it is likely that miR-126 [396] also mediates the close association between the neurogenic and angiogenic effects of mechanical stimulation [397–400]. Further details on miRs associated with proangiogenic activity (miR-9b, miR-10b [401], let-7b, let-7f [402], miR-17-92 cluster [403], miR-21-5p [404], miR-23, miR-27 [405], miR-106b-25 cluster [406], miR-126 [385,407], miR-132 [408], miR-135b [409], miR-210 [410], miR-296 [411], miR-378 [412]) can be found in a recent review [413].

While treatment based only on growth factors is unlikely to prevent death or major limb amputation and may not improve walking, ulceration, and rest pain, it may improve hemodynamic measures and decrease the rate of minor amputations in people with peripheral arterial disease [414].

5.2. Peripheral Nerve Repair

While regeneration of efferent motor nerves has direct implications on movement control, restoring the pathways of afferent signals impacts the somatosensory system, the motor system, and their connections. The cell bodies of peripheral nerves sit in DRG, and their axons split into peripheral and central branches with ultrastructural differences that are likely responsible for the higher transport rates and regenerative abilities of the peripheral branch [415].

Axon growth during peripheral nerve repair of adult cells requires the formation of growth cones [416]. After an injury, the influx of Ca^{2+} into the axoplasm [417,418] triggers a depolarizing wave from the axon to the soma, causing a change in the gene expression of the neuron [419,420]. While the soma sends messenger RNA to the injured area [421], the local accumulation of Ca^{2+} triggers calpain-dependent resealing of the cell membrane [422] through calcium-regulated proteins [423] and growth cone formation [418,424,425]. Several cells, especially Schwann cells, work with factors to support nerve regeneration.

Schwann cells are essential for proliferation, development of tubular guidance structures, and secretion of growth factors [426,427]; for example, measured after peripheral nerve repair, the number of Schwann cells was 17 times higher than in uninjured nerves [428]. Both nonmyelinating and myelinating Schwann cells are essential for myelin sheath production, maintenance, and peripheral nerve regrowth [429,430]. Distinct sensory and motor phenotypes [431] control the local axon protein synthesis by supplying ribosomes to axons that lost connection to the soma [432]. Thereby, the extracellular matrix, cell adhesion molecules, the cortical cytoskeleton, YAP/TAZ-signaling in adult nerve homeostasis [433], and extracellular and intracellular mechanical cues [434,435] play essential roles in the regulation of Schwann cell activity [436]. However, the related mechanically activated ion channels are not yet known [87]. They also process inputs from neurons and work with macrophages, fibroblasts, endothelial, and inflammatory cells to remove myelin debris and downregulate myelin proteins during Wallerian degeneration [437]. In the subsequent axon regeneration, VEGF-induced, polarized vasculature guides the regrowth of axons along bands of Büngner [416,438]. Considering the blood supply of peripheral nerves

and Schwann cells, it is not surprising that VEGF also promoted Schwann cell migration and neurite growth [427,439,440]. In addition, angiogenic activity and anti-inflammatory effects of the hepatocyte growth factor (HGF) after peripheral nerve injury in mice [441] supported neurite growth because of explicitly upregulated levels of HGF receptor c-met in Schwann cells [427,442]. However, Schwann cells may attack and destroy lymphatic endothelial cells, as was shown in 3D fibrin hydrogels in vitro [443].

Keratinocytes in the skin produce and secrete many neuroactive factors [444–449] in close association with intraepidermal nerve endings [83,450–452]. The neurotrophic factors nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3), and NT-4/5, together with the epidermal growth factor (EGF), may affect immunoreactivity in Meissner and Pacinian corpuscles and their associated LTMRs in an age-specific manner [187]. Sequencing data at 0 h, 1 d, 4 d, 7 d, and 14 d after rat sciatic nerve crush injury revealed time-specific patterns of the expression of several neurotrophic growth factors. The well-known growth factors BDNF and NGF, but also neuregulin 1 (NRG1) and inhibin subunit beta A (INHBA), remained upregulated at all times [453]. While increased NRG1 indicates the regenerative activity of Schwann cells [454], the biological function of INHBA is not well understood. BDNF stimulates Schwann cells to produce proregenerative cytokines specifically [427,455], and may be more specific to the outgrowth of parasympathetic nerves, e.g., the nerves of the nodose ganglion [456]. NGF is associated with inflammatory and anti-inflammatory effects [457] and seems specific to peripheral sympathetic and neural-crest-derived sensory neurons [456]. GDNF, associated with neuronal survival and repair [458], was upregulated until 7 d [453]. Both NT-3 and NT-4 are closely related to BDNF and NGF but were not consistently active over time: NT-3 was only downregulated at 1 d, and NT-4 was upregulated at 4 d but downregulated at 14 d [453]. Other studies showed that NT-3 triggers neurite outgrowth in sympathetic and parasympathetic systems [459]. Moreover, injections with NT-3 improved sensory modalities, e.g., a specific effect on the Ia muscle spindle afferents [460,461]. Thus, the effect of neurotrophic factors during axon regeneration depends on the time and location of the sample, and one has to consider if neurotrophic factors were injected artificially or were released naturally.

Growth factors and mechanical cues affect peripheral nerve repair. Using cultured dopaminergic sympathetic ganglion neuron cells (PC12 cells treated with M3 and NGF) [462,463], vibration from 7–100 Hz enhanced neurite outgrowth when compared to NGF alone (Figure 3) [224,225]. Thereby, Piezo1 is important for axon growth because its knockdown induced aberrant growth and pathfinding errors [464]. In brain models of *Xenopus* RGC frogs, increased brain stiffness promoted Piezo1-guided faster, straighter, and more parallel axon growth in vitro and in vivo. Thus, extracellular forces [465] and mechanical forces within the growth cone guided axon growth [466] to follow areas of tension [467].

In contrast, mechanically activated Piezo1 signaling in mouse peripheral axon growth cones initiated signaling cascades that inhibit axon growth [468], i.e., Piezo1 enrichment in *Drosophila* flies axon growth cone after an injury increased growth-inhibitory Ca^{2+} release, NO synthase (NOS) activity, and NO signaling [45,468]. Thereby, the differences in the species, the cell types used, or cell origin, i.e., central vs. peripheral nervous system, may explain the diverging roles of Piezo1 activation that either promoted central [224,225,464] or inhibited peripheral axon growth [45,468]. For example, the activity of the three mammal isoforms of NOS may have affected the results, where inducible NOS (iNOS) and neuronal NOS (nNOS) are known to contribute to axon regeneration during Wallerian degeneration; however, eNOS inhibits axon regrowth, at least soon after injury [469].

In peripheral nerves, several miRs also regulate extracellular matrix remodeling, axon growth, intracellular signaling, proliferation, migration, cell adhesion, and neurogenesis [470–473]. miRs play roles in neurological disorders including Alzheimer's, Parkinson's, stroke, epilepsy, multiple sclerosis, amyotrophic lateral sclerosis, and Huntington's [474]. For example, while miR let-7 and miR-9 regulate axon outgrowth and pathfinding during peripheral nerve regeneration through the NF- κ B pathway [475], several other miRs have regulatory effects on axon repair (miR-1 [476], miR-1b [477,478], miR-9 [479], miR-

9/let-7 family [475], let-7 [480], Lin28/let-7-axis [481], miR-21 [482,483], miR-30c [484], miR-34a [485,486], miR-124 [487], miR-129 [488], miR-132 [489], miR-138 [490], miR-140 [486], miR-146b [491], miR-182 [492], miR-192 [493], miR-210 [494], miR-221/222 [492,495], miR-340 [496], miR-485-5p [497], miR-3075 [498], miR-3099 [499]) that activate or inhibit neurogenic pathways [473]. Further details on the effects of low cellular forces in the nervous system, and on peripheral nerve repair, are described in recent reviews in detail [416,500,501].

While focal vibration therapy leverages these mechanisms to promote nerve recovery, more and more sensory information becomes available for central processing. Subsequently, the increasing influx of information to the brain activates the related pathways and areas. However, the signal's quality should also be considered to achieve functional physiological adaptations.

6. Neuromodulation Effects of Focal Vibration

Promoting nerve recovery and directly stimulating the senses of touch and body position with physiologically adequate stimuli, focal vibration therapy creates and affects sensory inputs to the brain. This section establishes the connection between the somatosensory and motor system, autonomous nervous system, and clinical outcomes of focal vibration therapy.

Vibratory sensory feedback utilizes the senses of touch and proprioception that are critical for balance, motor and postural control, hand grip, and the detection and manipulation of objects [54,191,502,503]. Its neuromodulatory effect can be a crucial enabler of recovery, homeostasis, and assistive device use, e.g., exoprostheses [504–508], and improves embodiment and agency. Embodiment is the experience of owning one's body (part) [509], which can be affected when a person experiences a mismatch between vision and other sensory inputs [510,511]. Agency is the experience of authorship of one's movement, which may change with the loss of peripheral sensation [512] when cognitive or emotional reactions to unfamiliar perceptions affect the mutual integration of the internal model of movement, visual feedback, and movement sensation [513–515]. Thereby, the variance of the haptic feedback prediction may exceed that of the visual channel, which will increase the reliance upon vision [516]. Since both agency and embodiment contribute to body awareness [517,518], vibrotactile feedback potentially affects the spatial mapping of “telescoping” or shortening phantom limb perceptions [519,520]. Thus, vibrotactile feedback can be a noninvasive method for restoring sensation for people who have lost peripheral afferent sensory signals through disease or traumatic injury [521].

Functionally, the loss of peripheral sensation can change the cortical topography of the highly interconnected primary and secondary sensorimotor areas. Even in the absence of pain, the loss of inhibiting afferent neural inputs may reduce the functional connectivity between the primary (S1) and secondary (S2) somatosensory areas, as well as between the primary (M1) and secondary (M2) motor areas. While their functional connectivity may decrease on the side of the amputation, it may also increase on the contralateral side [522]. S1 is divided into the three Brodmann areas (BA) 1, 2, 3a, and 3b. In monkeys, BA3 receives most thalamocortical projections [523], where BA3b is specifically responsive to RA1-, SA1-, and SA2-LTMRs [173]. The processing of signals in the sensorimotor network is complex, and peripheral sensory stimulation can trigger unexpected responses. For example, ~75% of sensorimotor stimulations evoke typical contralateral responses [524–527]. However, in atypical cases, stimulation of S1 may evoke a motor response, and stimulation of M1 may induce contralateral sensory perceptions [173,528]. Figure 4 summarizes the interaction of focal vibration therapy with the central nervous system and its possible systemic effects.

In neurological and psychiatric conditions, vibratory sensory stimulation may positively influence pain [529]. For example, improving thalamocortical dysrhythmia, caused by dysrhythmic activation of sensorimotor areas, may explain suggested positive outcomes of 40 Hz vibrotactile stimulation in patients with fibromyalgia (Figure 3) [96,218]. Similar to previous studies in people with pain related to temporomandibular disorder [530,531], one week of 16 min daily 100 Hz vibration of the painful area of the jaw reduced joint pain, mus-

cular pain, and headache (Figure 3) [219]. In addition, phantom limb pain is associated with the loss of afferent signals, invasion of neighboring cortical areas, and further structural and functional changes in the cortical representation of the disconnected periphery [244,245]. Attempts to counteract such maladaptation with tactile feedback showed that sensory stimulation of skin areas associated with the lost body part helped with pain and promoted cortical reorganization [243]. Unfortunately, residual limb pain and painful neuromas also occur in 59% and 15% of people with lower limb amputations, respectively [532], posing challenges to the treatment strategies that affect central and peripheral causes simultaneously. Nevertheless, treating these origins of pain could promote central desensitization of hyperexcitable spinal neurons and help with allodynia, hyperalgesia, and spontaneous pain [246].

Focal vibration therapy can also positively affect motor control and locomotion. For example, the frequency range from 75–120 Hz affected motor control [221] and improved walking speed [222]. Subthreshold vibration improved balance in people with unilateral transtibial amputations but did not change measures of somatosensation [533]. Calf muscle vibration at 120 Hz, 1.2 mm improved chair rises, timed up-and-go test, and 6 min walk test in people with peripheral artery disease [534]. Using 35–120 Hz vibrations improved outcomes in the standard and cognitive timed up-and-go test and short pain memory in people with diabetic peripheral neuropathy [223]. Similarly, after four weeks of 120 Hz, 1.2 mm focal vibration therapy, gait speed, cadence, stride time, left and right stance time, duration of double limb support, and left and right knee flexion moments improved (Figures 2 and 3) [73]. While there was no immediate effect of tendon vibration on neural drive [57], physical training for 20–60 min with muscle tendon vibration at 50–120 Hz, 1 mm increased motor evoked potentials and cortical excitability [216]. In people with stroke, the frequency range between 85–120 Hz with amplitudes from 0.01–2 mm reduced spasticity (Figures 2 and 3) [275]. In addition, adding 20 min of individualized vibration frequency up to 60 Hz to 45 min conventional stroke rehabilitation of the affected upper limb in nine patients for six weeks and three times a week improved sensation, motor function, and movement scores compared to the control group [535]. In people with cerebral palsy, vibration therapy (whole body vibration and focal vibration applied to the targeted muscle belly and tendon) had positive short-term effects for up to 30 min on gross motor function, strength, gait, and mobility [330]. Thereby, long-term effects were improved gait and mobility through improved strength, reduced muscle tone and spasticity, and increased muscle mass and bone mineral density. However, postural control did not change. This is well summarized in the conclusion of a recent umbrella review of systematic reviews, stating that vibration therapies in neurological diseases

“[...] appear to play a considerable role in reducing spasticity and improving gait, balance, and motor function in patients affected by stroke. In particular, focal muscle vibration [was] more useful if applied to nonspastic antagonist muscles with reciprocal inhibitory action on spastic muscles. Conversely, vibration therapy seems [unable] to reduce spasticity in multiple sclerosis and cerebral palsy. Concerning spinal cord injury, Parkinson’s disease, spinocerebellar ataxia, dystonia, and essential tremor, no evidence-based recommendation could be drawn from the literature to guide rehabilitation medicine clinicians to manage spasticity with vibration application” (Moggio et al. [242]).

6.1. Vibratory Sensory Feedback

Having lost essential sensory abilities, people with amputations often struggle with fine motor tasks [536], embodiment [537], and psychosocial distress [538], together increasing the probability of device abandonment and a sedentary lifestyle [537,539,540]. Sensory feedback can provide tactile information for people with amputations [538,541–546] and can reduce the risk of falls in patients with peripheral sensory neuropathy through improved gait and balance [547,548]. Thus, providing sensory feedback for people with

sensory impairments can increase confidence, mobility, and functionality while decreasing fatigue and physical exertion (Figure 4) [503,541,549–555].

To create adequate and physiological sensory signals, it is crucial to apply the feedback to an area that a person has either already associated with the missing area or one that will most likely become a sensory substitute. Such a sensory map of a phantom limb enables a person with an amputation to experience touch, force, vibration, temperature, and pain in a skin area that they associate with the missing limb [235]. Such long-lasting maps may evolve naturally [556] or through targeted sensory reinnervation surgery during amputation- or pain/neuroma-indicated post-amputation surgery where surgeons connect sensory nerve fibers to skin areas [557–562].

Applying vibrotactile feedback to sensory maps can have several positive effects. Providing two participants with proprioceptive and touch feedback via 90 Hz, 1 mm vibration to the sensory maps of their missing hands helped reduce reliance on visual control [563]. Three subjects with upper limb amputations who received kinesthetic feedback through 70–110 Hz muscle vibration improved in movement control scores within minutes (Figures 2 and 3) [68]. When mapping logarithmic total insole pressure to vibrotactile cues at 0.1, 0.3, and 0.5 Hz, four participants with transtibial amputations improved postural stability [220]. Similarly, gait, balance, and pain scores improved in four participants with lower limb amputations following targeted sensory reinnervation and training with vibrotactile feedback [564].

Five patients who underwent targeted muscle and sensory reinnervation and later received feedback from their hand prosthesis via implanted electrodes connected to sensory fibers of the median and ulnar nerves improved in synaptic strength and connectivity of the sensorimotor network, and reduced phantom limb pain occurred in three out of four affected patients [565]. Similarly, somatosensory feedback mapping of thumb–index finger contact pressure to electrical stimuli reduced pain in all eight participants with transradial amputation [566] and another three patients gained cortical plasticity in M1, partially in S1, and their mutual connectivity [567]. Such a neural reorganization within the central nervous system likely contributed to reductions in phantom limb pain and improvements in gait, posture, prosthesis dexterity, and device satisfaction in 14 unilateral lower limb amputees who received electrocutaneous feedback of ground contact [568].

By integrating afferent sensory feedback from the skin, muscle spindle receptors, and Golgi tendon organ, illusory movement sensations can be created (Figure 1) [54,70,569] that could promote sensory integration in therapies for persons who cannot move or sense naturally. For example, vibrotactile stimulation at 100 Hz with an amplitude of 0.5 mm created perceptions of illusory movement and muscle stretch at various joints [69]. While 100 Hz vibration with 1 mm amplitude already induced perceptions of illusory movements at the index finger, elbow, and knee, adding skin stretch amplified the perception even further (Figure 2) [70]. Similarly, mapping cursor position feedback to 250 Hz vibration with accelerations between 0 and 7.5 G or to skin stretch showed smaller position errors for skin stretch than vibration alone [570].

Thus, the signal quality and application area should be considered when considering vibrotactile feedback. By activating large networks in the brain and promoting an active lifestyle, vibrotactile feedback will also stimulate the body's regulatory systems.

6.2. Effects on the Autonomous Nervous System

Improving a person's ability to walk and experience the surroundings should promote exercise, stimulating the autonomic nervous system. Since 140 Hz vibrotactile stimulation directly over the hand and finger flexor muscles already increased heart rate and heart rate variability, vibrotactile muscle stimulation could modulate the autonomic system (Figure 3) [226]. In addition, exercise as a form of autonomic system nerve stimulation is tempting. For example, targeted stimulation of the autonomic system paired with physical exercise facilitated motor recovery after neurological injuries [240,571–575], and pairing vagus nerve stimulation with tactile rehabilitation improved somatosensory function [576,

577]. In rats with ischaemic stroke, neuroprotective, neurogenic, and anti-inflammatory effects of long-term 28 days' vagus nerve stimulation were associated with increased brain levels of BDNF [578], growth differentiation factor 11 (GDF-11) [399,579], eNOS, VEGF, and PPAR- γ [580], as well as with improved neurological outcomes, including accelerated central axon regeneration and reorganization [241,578,579]. Thus, exercise, feedback, and focal vibration therapy could complement each other, especially if triggering the vagus nerve regenerative processes (Figure 4).

6.2.1. Vagus Nerve

The vagus nerve is part of the parasympathetic system with afferent and efferent fibers emerging from the medulla [182,581–583]. The parasympathetic system, and especially the vagus nerve, is essential for controlling, adapting, and regenerating the body. About 20% of vagus fibers are efferent and modulate autonomic processes, including the control of blood pressure [584], heart rate, gastrointestinal motility [585], vascular resistance, airway diameter, and respiration [239]. Its afferent fibers carry information from almost every organ—including pressure, pain, muscular tension, temperature, chemical, osmotic pressure, and inflammation—to the nucleus of the solitary tract that lies in the medulla oblongata [239,586]. Upon inflammation, the vagus nerve modulates the parasympathetic system, and in concert with the sympathetic system [587], both controlling essential immune organs, including the spleen, adrenal glands, and possibly bone marrow [588–591]. Thus, vagus nerve stimulation may also benefit patients with inflammatory diseases [585].

Even though stimulation of the vagus nerve is generally associated with a reduction of pain [590], its afferent fibers have inhibitory *and* excitatory effects on the pain processing in the spinal cord (Figure 4) [592–594]. Stimulation of the vagus nerve increases the activity of the locus coeruleus and raphe neurons [595,596]. The subsequent release of noradrenaline from the locus coeruleus and serotonin from raphe neurons enhances the plasticity of sensory networks [240]. This release of noradrenaline and serotonin increases the gain for synaptic inputs, thus, likely facilitating the activity of persistent inward currents and subsequent motor unit activity [597,598]. Together, these processes may support a cortical reorganization in people with restored sensory feedback. Furthermore, sensing elevated blood pressure and breath during exercise may be a positive amplifier for regenerative processes.

The vagus nerve stimulation is functionally associated with the vagal nodose and petrosal sensory neurons that coexpress Piezo1 and Piezo2 and work in concert with mechanosensitive nerve endings in arterial walls to detect stretch of the aorta and the carotid sinus [2,28,33,599]. Excitatory glutaminergic fibers transmit baroreceptor signals through monosynaptic pathways to the nucleus of the solitary tract that integrates them with inputs from the heart and chemoreceptors [600]. The nucleus of the solitary tract also controls cardioinhibitory pathways and peripheral vascular resistance through inhibitory GABAergic interneurons that inhibit sympathoexcitatory glutaminergic neurons [91]. For example, detecting rising blood pressure during muscle contractions, the nucleus of the solitary tract reduces sympathetic outflow, decreases cardiac output and heart rate [27,91,584], and increases skin blood flow and vasodilation in skeletal muscles [599]. However, other sensory and autonomous nervous systems are involved in these regulatory processes [33,239,599] that are additionally modulated by attention.

6.2.2. Ascending Reticular Activating System

Restoring sensory pathways of lost body parts most likely restores and increases a person's attention to that area. The ascending reticular activating system (ARAS) controls processes related to attention. Thereby, the ascending and descending pathways of the reticular formation regulate the activity of the thalamocortical area, arousal, and sleep–wake cycles [601]. The reticular formation extends from the medulla to the hypothalamus, connects to most brain regions, is essential in the involuntary regulation of breathing and blood circulation [238,602], and affects voluntary motor actions (Figure 4) [183,603–607].

The ARAS includes the noradrenergic locus coeruleus located in the pons of the brain-stem, known to influence the level of attention, alertness, brain metabolism, gene expression, and brain inflammatory processes [183]. Stimulation of the locus coeruleus increases glutamate/norepinephrine-mediated motoneuron excitability [608] and inhibits α 2-adrenergic-receptor-modulated (acute) pain perception [609]. During motor learning, the locus coeruleus can adjust the intensity of the vestibulospinal and vestibulo-ocular reflex to the level of the arousal [610–612]. The locus coeruleus–noradrenaline pathway affects the synaptic plasticity of the amygdala and hippocampus, mediates memory processes [613–615], and triggers the synthesis and release of astrocytic BDNF [616,617] which may explain long-term cognitive improvements following physical exercise [618]. Thus, the ARAS seems to be highly engaged in the recovery of brain areas during motor rehabilitation and should be essential for developing phantom limb maps. For example, while short periods of discharge and silence synchronize large portions of the thalamocortical area [619], neighboring populations of neurons synchronize their firing patterns during long periods of simultaneous discharge [620] or those involved in the same task [621]. The latter may involve Hebb’s rule in the formation of phantom limb maps [622], because

“neurons wire together if they fire together” (Löwel and Singer [623]).

Consequently, peripheral sensory stimulation may improve sensorimotor [624] and cognitive functions [625] and may mitigate symptoms of some brain pathologies [183]. For example, by promoting neuroplasticity [626], neuroregeneration, and neural repair [182,627], neuromodulation techniques could counteract reductions of gray matter in people with upper limb amputations [628] as well as white matter changes in people with lower limb amputations [629]. As the posterior parietal and premotor cortex process afferent sensory feedback for prediction and planning purposes, and S1 and M1 process immediate feedback, enhanced sensory feedback can also cause adaptations in sensorimotor networks that may improve agency and embodiment (Figure 4) [173,630,631].

7. Conclusions

Focal vibration applied as sensory feedback can reduce pain and increase safety during walking, as well as provide the acceptance of an assistive device as one’s body part while avoiding adverse effects. While focal vibration therapy supports the health of blood vessels and nerves locally (Figure 6), it stimulates sensory nerves and their pathways up to the brain, triggering beneficial physiological adaptations centrally (Figure 4).

When applying focal vibration to a skin area above skeletal muscles, mechanically activated Piezo ion channels trigger signaling pathways that positively affect local blood vessels and peripheral nerves. Mechanical activation of Piezo channels during physical exercise stimulates the interplay between sympathetic and parasympathetic nervous systems, affecting muscle contractions and usually increasing blood pressure, heart rate, and blood flow in muscles and skin [35,599,632]. Thus, physical exercise and focal vibration can increase the laminar flow and shear stress in blood vessels that trigger protective molecular signaling cascades in arteries (Figure 6) [34,65,366,632]. This is supported by several metabolic factors that facilitate the repair of blood vessels, skin, muscles, and nerves [15,124,591]. Axon repair [396], Schwann cell migration, and axon growth [416,427,438–440] are supported by neural and vascular growth factors [397–399], because peripheral nerves rely on axonal transport and blood vessels for supply [395]. However, after amputation, undirected peripheral nerve growth can contribute to the development of painful neuromas [532,560]. While neuroma growth could be slowed due to a growth-inhibitory effect of mechanical Piezo1 activation in nerve growth cones, the current evidence is limited to *Drosophila* flies and adult mice [45,468].

Vibratory stimulation of the sense of touch, body position, and Piezo2 [31,74] has systemic effects on the central nervous system that are beneficial for the periphery. Closely matching somatosensory feedback with physiological patterns of manual dexterity or ground contact will most likely achieve adequate stimuli for effective sensorimotor rehabilitation and pain management. This is made possible through the interrelated processing

of touch and pain in the dorsal horn that allows touch to modulate and eventually reduce pain [181,217,236,237]. In the long term, neuromodulation can drastically reduce phantom limb pain by recovering the physiological organization and function of the somatosensory and motor cortex network [243–245]. Through these mechanisms, focal vibration therapy helped people with chronic regional pain syndrome [71], neuropathic pain [50,83,218,223,246], and hypersensitivity [72]. Reducing pain, activating the ascending arousal system [608,609], recovering somatosensory and motor cortex function [624], stimulating the regenerative capacity of the vagus nerve [226,240,571–577], and improving agency and embodiment through restored sensation [516], vibrotactile feedback can promote physical activity and active participation in social life (Figure 4).

The selection of adequate vibration settings is crucial for achieving the desired therapeutic effects of focal vibration therapy. The frequency of use and the technical amplitude, frequency, and acceleration or force of vibration should follow proven principles of focal vibration therapy in humans. We recommend using stimulation parameters between ~60–120 Hz and up to 1 mm for vibrotactile feedback. These showed positive effects of vibrotactile stimulation on locomotion [221–223], pain [71,72,217,219,223], blood vessels [66,67], corticospinal excitability [216], and mostly harmonic one-to-one transduction of vibration by muscle spindles [59–62,68,216], while adverse effects are possible at >125 Hz [214] (Figures 1 and 2). These ranges were studied in >65% of the articles listed in nine systematic reviews on focal muscle or tendon vibration therapy [268–276] (Figure 5).

Providing vibratory feedback in those settings could benefit, e.g., the residual limb management of atrophy, blood flow, and skin health. Thus, studies should report the effective vibration parameters applied to the specified application area, including amplitude, frequency, and intensity quantified as force or acceleration [633]. Future studies should establish the direct link between vibration therapy and its short-term effects, including NO production, hemodynamics, growth factors, miRs, reflex pathways of motor unit recruitment; and long-term effects, including changes in the somatosensorimotor area and the histology of nerves and blood vessels. Randomization, placebo/sham conditions, and single- or double-blinded designs should become standard for further testing the effectiveness of vibrotactile feedback therapy in clinical and post-clinical settings.

Author Contributions: Conceptualization, H.P. and G.P.; methodology, H.P.; software, H.P.; validation, H.P., F.P. and G.P.; formal analysis, H.P.; investigation, H.P.; resources, H.P.; data curation, H.P.; writing—original draft preparation, H.P.; writing—review and editing, H.P. and F.P.; visualization, H.P.; supervision, G.P.; project administration, G.P.; funding acquisition, G.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: We thank Alena Grabowski for providing initial and revision comments, Kevin Mandagere for checking the abstract and the conclusions, and Wolfgang Schaden for his encouragement. Figures 4 and 6 were created with BioRender.com (accessed on 28 November 2022) under paid subscription.

Conflicts of Interest: H.P. and F.P. were financially supported by Saphenus Medical Technology. G.P. is the scientific head of the research project FK 31/19 “Sensoric in Exoprosthetic” sponsored by AUVA and Saphenus Medical Technology since 2019. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Abbreviations

The following abbreviations are used in this manuscript:

AKT	protein kinase B
ARAS	ascending reticular activating system
BDNF	brain-derived neurotrophic factor
bFGF	basic fibroblast growth factor
BA	Brodman areas
DRG	dorsal root ganglion
EGF	epidermal growth factor
eNOS	endothelial nitric oxygen synthase
GDNF	glial-derived neurotrophic factor
HGF	hepatocyte growth factor
INHBA	inhibin subunit beta A
iNOS	inducible nitric oxygen synthase
LTMR	low-threshold mechanoreceptors
M1 2	primary secondary motor area
miR	micro RNA
NF-κB	nuclear factor κB
NGF	nerve growth factor
nNOS	neuronal nitric oxygen synthase
NO	nitric oxygen
NOS	nitric oxygen synthase
NRG1	neuregulin 1
NT	neurotrophin
RA	rapidly adapting
S1 2	primary secondary somatosensory area
S1P	sphingosine 1 phosphate
SA	slowly adapting
TAZ	transcriptional coactivator with PDZ-binding motif
TRP	transient receptor potential
VEGF	vascular endothelial growth factor
VEGFR	VEGF receptor
YAP	Yes-associated protein

References

1. Müller-Oerlinghausen, B.; Eggart, M.; Norholt, H.; Gerlach, M.; Kiebgis, G.M.; Arnold, M.M.; Moberg, K.U. Touch Medicine—A complementary therapeutic approach exemplified by the treatment of depression. *Dtsch. Med. Wochenschr.* **2022**, *147*, E32–E40. [[CrossRef](#)] [[PubMed](#)]
2. Coste, B.; Mathur, J.; Schmidt, M.; Earley, T.J.; Ranade, S.S.; Petrus, M.J.; Dubin, A.E.; Patapoutian, A. Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. *Science* **2010**, *330*, 55–60. [[CrossRef](#)] [[PubMed](#)]
3. Beech, D.J.; Kalli, A.C. Force Sensing by Piezo Channels in Cardiovascular Health and Disease. *Arterioscler. Thromb. Vasc. Biol.* **2019**, *39*, 2228–2239. [[CrossRef](#)] [[PubMed](#)]
4. Guo, Y.R.; MacKinnon, R. Structure-based membrane dome mechanism for piezo mechanosensitivity. *eLife* **2017**, *6*, 1–19. [[CrossRef](#)] [[PubMed](#)]
5. Saotome, K.; Murthy, S.E.; Kefauver, J.M.; Whitwam, T.; Patapoutian, A.; Ward, A.B. Structure of the mechanically activated ion channel Piezo1. *Nature* **2018**, *554*, 481–486. [[CrossRef](#)] [[PubMed](#)]
6. Zhao, Q.; Zhou, H.; Chi, S.; Wang, Y.; Wang, J.; Geng, J.; Wu, K.; Liu, W.; Zhang, T.; Dong, M.Q.; et al. Structure and mechanogating mechanism of the Piezo1 channel. *Nature* **2018**, *554*, 487–492. [[CrossRef](#)]
7. Lin, Y.C.; Guo, Y.R.; Miyagi, A.; Levring, J.; Mackinnon, R.; Scheuring, S. Force-induced conformational changes in PIEZO1. *Nature* **2019**, *573*, 230–234. [[CrossRef](#)]
8. Wang, L.; Zhou, H.; Zhang, M.; Liu, W.; Deng, T.; Zhao, Q.; Li, Y.; Lei, J.; Li, X.; Xiao, B. Structure and mechanogating of the mammalian tactile channel PIEZO2. *Nature* **2019**, *573*, 225–229. [[CrossRef](#)]
9. Geng, J.; Liu, W.; Zhou, H.; Zhang, T.; Wang, L.; Zhang, M.; Li, Y.; Shen, B.; Li, X.; Xiao, B. A Plug-and-Latch Mechanism for Gating the Mechanosensitive Piezo Channel. *Neuron* **2020**, *106*, 438–451.e6. [[CrossRef](#)]

10. Szczot, M.; Nickolls, A.R.; Lam, R.M.; Chesler, A.T. The Form and Function of PIEZO2. *Annu. Rev. Biochem.* **2021**, *90*, 507–534. [\[CrossRef\]](#)
11. Bagriantsev, S.N.; Gracheva, E.O.; Gallagher, P.G. Piezo Proteins: Regulators of Mechanosensation and Other Cellular Processes. *J. Biol. Chem.* **2014**, *289*, 31673–31681. [\[CrossRef\]](#)
12. Murthy, S.E.; Dubin, A.E.; Patapoutian, A. Piezos thrive under pressure: Mechanically activated ion channels in health and disease. *Nat. Rev. Mol. Cell Biol.* **2017**, *18*, 771–783. [\[CrossRef\]](#)
13. Wu, J.; Lewis, A.H.; Grandl, J. Touch, Tension, and Transduction—The Function and Regulation of Piezo Ion Channels. *Trends Biochem. Sci.* **2017**, *42*, 57–71. [\[CrossRef\]](#)
14. McCarter, G.C.; Reichling, D.B.; Levine, J.D. Mechanical transduction by rat dorsal root ganglion neurons in vitro. *Neurosci. Lett.* **1999**, *273*, 179–182. [\[CrossRef\]](#)
15. Retailliau, K.; Duprat, F.; Arhatte, M.; Ranade, S.S.; Peyronnet, R.; Martins, J.R.; Jodar, M.; Moro, C.; Offermanns, S.; Feng, Y.; et al. Piezo1 in Smooth Muscle Cells Is Involved in Hypertension-Dependent Arterial Remodeling. *Cell Rep.* **2015**, *13*, 1161–1171. [\[CrossRef\]](#)
16. Gaub, B.M.; Müller, D.J. Mechanical Stimulation of Piezo1 Receptors Depends on Extracellular Matrix Proteins and Directionality of Force. *Nano Lett.* **2017**, *17*, 2064–2072. [\[CrossRef\]](#)
17. Qiu, Z.; Guo, J.; Kala, S.; Zhu, J.; Xian, Q.; Qiu, W.; Li, G.; Zhu, T.; Meng, L.; Zhang, R.; et al. The Mechanosensitive Ion Channel Piezo1 Significantly Mediates In Vitro Ultrasonic Stimulation of Neurons. *iScience* **2019**, *21*, 448–457. [\[CrossRef\]](#)
18. Ellefsen, K.L.; Holt, J.R.; Chang, A.C.; Nourse, J.L.; Arulmoli, J.; Mekhdjian, A.H.; Abuwarda, H.; Tombola, F.; Flanagan, L.A.; Dunn, A.R.; et al. Myosin-II mediated traction forces evoke localized Piezo1-dependent Ca²⁺ flickers. *Commun. Biol.* **2019**, *2*, 1–13. [\[CrossRef\]](#)
19. Syeda, R.; Xu, J.; Dubin, A.E.; Coste, B.; Mathur, J.; Huynh, T.; Matzen, J.; Lao, J.; Tully, D.C.; Engels, I.H.; et al. Chemical activation of the mechanotransduction channel Piezo1. *eLife* **2015**, *4*, 1–11. [\[CrossRef\]](#)
20. Wang, Y.; Chi, S.; Guo, H.; Li, G.; Wang, L.; Zhao, Q.; Rao, Y.; Zu, L.; He, W.; Xiao, B. A lever-like transduction pathway for long-distance chemical- and mechano-gating of the mechanosensitive Piezo1 channel. *Nat. Commun.* **2018**, *9*, 1300. [\[CrossRef\]](#)
21. Kim, T.H.; Jeon, W.Y.; Ji, Y.; Park, E.J.; Yoon, D.S.; Lee, N.H.; Park, S.M.; Mandakhbayar, N.; Lee, J.H.; Lee, H.H.; et al. Electricity auto-generating skin patch promotes wound healing process by activation of mechanosensitive ion channels. *Biomaterials* **2021**, *275*, 120948. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Huang, J.Q.; Zhang, H.; Guo, X.W.; Lu, Y.; Wang, S.N.; Cheng, B.; Dong, S.H.; Lyu, X.L.; Li, F.S.; Li, Y.W. Mechanically Activated Calcium Channel PIEZO1 Modulates Radiation-Induced Epithelial-Mesenchymal Transition by Forming a Positive Feedback With TGF- β 1. *Front. Mol. Biosci.* **2021**, *8*, 972. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Hao, L.; Li, L.; Wang, P.; Wang, Z.; Shi, X.; Guo, M.; Zhang, P. Synergistic osteogenesis promoted by magnetically actuated nano-mechanical stimuli. *Nanoscale* **2019**, *11*, 23423–23437. [\[CrossRef\]](#)
24. Gnanasambandam, R.; Bae, C.; Gottlieb, P.A.; Sachs, F. Ionic selectivity and permeation properties of human PIEZO1 channels. *PLoS ONE* **2015**, *10*, e0125503. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Coste, B.; Xiao, B.; Santos, J.S.; Syeda, R.; Grandl, J.; Spencer, K.S.; Kim, S.E.; Schmidt, M.; Mathur, J.; Dubin, A.E.; et al. Piezo proteins are pore-forming subunits of mechanically activated channels. *Nature* **2012**, *483*, 176–181. [\[CrossRef\]](#)
26. Qin, L.; He, T.; Chen, S.; Yang, D.; Yi, W.; Cao, H.; Xiao, G. Roles of mechanosensitive channel Piezo1/2 proteins in skeleton and other tissues. *Bone Res.* **2021**, *9*, 1–17. [\[CrossRef\]](#)
27. Shah, V.; Patel, S.; Shah, J. Emerging role of Piezo ion channels in cardiovascular development. *Dev. Dyn.* **2022**, *251*, 276–286. [\[CrossRef\]](#)
28. Douguet, D.; Patel, A.; Xu, A.; Vanhoutte, P.M.; Honoré, E. Piezo Ion Channels in Cardiovascular Mechanobiology. *Trends Pharmacol. Sci.* **2019**, *40*, 956–970. [\[CrossRef\]](#)
29. Gilchrist, C.L.; Leddy, H.A.; Kaye, L.; Case, N.D.; Rothenberg, K.E.; Little, D.; Liedtke, W.; Hoffman, B.D.; Guilak, F. TRPV4-mediated calcium signaling in mesenchymal stem cells regulates aligned collagen matrix formation and vinculin tension. *Proc. Natl. Acad. Sci.* **2019**, *116*, 1992–1997. [\[CrossRef\]](#)
30. Murthy, S.E.; Loud, M.C.; Daou, I.; Marshall, K.L.; Schwaller, F.; Kühnemund, J.; Francisco, A.G.; Keenan, W.T.; Dubin, A.E.; Lewin, G.R.; et al. The mechanosensitive ion channel Piezo2 mediates sensitivity to mechanical pain in mice. *Sci. Transl. Med.* **2018**, *10*, eaat9897. [\[CrossRef\]](#)
31. Szczot, M.; Liljencrantz, J.; Ghitani, N.; Barik, A.; Lam, R.; Thompson, J.H.; Bharucha-Goebel, D.; Saade, D.; Necaie, A.; Donkervoort, S.; et al. PIEZO2 mediates injury-induced tactile pain in mice and humans. *Sci. Transl. Med.* **2018**, *10*, eaat9892. [\[CrossRef\]](#)
32. Ranade, S.S.; Qiu, Z.; Woo, S.H.; Hur, S.S.; Murthy, S.E.; Cahalan, S.M.; Xu, J.; Mathur, J.; Bandell, M.; Coste, B.; et al. Piezo1, a mechanically activated ion channel, is required for vascular development in mice. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 10347–10352. [\[CrossRef\]](#)

33. Zeng, W.; Marshall, K.L.; Min, S.; Daou, I.; Chapleau, M.W.; Abboud, F.M.; Liberles, S.D.; Patapoutian, A. PIEZO2 mediate neuronal sensing of blood pressure and the baroreceptor reflex. *Science* **2018**, *362*, 464–467. [\[CrossRef\]](#)
34. Wang, S.P.; Chennupati, R.; Kaur, H.; Iring, A.; Wettschureck, N.; Offermanns, S. Endothelial cation channel PIEZO1 controls blood pressure by mediating flow-induced ATP release. *J. Clin. Investig.* **2016**, *126*, 4527–4536. [\[CrossRef\]](#)
35. Rode, B.; Shi, J.; Endesh, N.; Drinkhill, M.J.; Webster, P.J.; Lotteau, S.J.; Bailey, M.A.; Yuldasheva, N.Y.; Ludlow, M.J.; Cubbon, R.M.; et al. Piezo1 channels sense whole body physical activity to reset cardiovascular homeostasis and enhance performance. *Nat. Commun.* **2017**, *8*, 350. [\[CrossRef\]](#)
36. Nonomura, K.; Lukacs, V.; Sweet, D.T.; Goddard, L.M.; Kanie, A.; Whitwam, T.; Ranade, S.S.; Fujimori, T.; Kahn, M.L.; Patapoutian, A. Mechanically activated ion channel PIEZO1 is required for lymphatic valve formation. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 12817–12822. [\[CrossRef\]](#)
37. Choi, D.; Park, E.; Jung, E.; Cha, B.; Lee, S.; Yu, J.; Kim, P.M.; Lee, S.; Hong, Y.J.; Koh, C.J.; et al. Piezo1 incorporates mechanical force signals into the genetic program that governs lymphatic valve development and maintenance. *JCI Insight* **2019**, *4*, 1–15. [\[CrossRef\]](#)
38. Faucherre, A.; Moha Ou Maati, H.; Nasr, N.; Pinard, A.; Theron, A.; Odelin, G.; Desvignes, J.P.; Salgado, D.; Collod-Bérout, G.; Avierinos, J.F.; et al. Piezo1 is required for outflow tract and aortic valve development. *J. Mol. Cell. Cardiol.* **2020**, *143*, 51–62. [\[CrossRef\]](#)
39. Duchemin, A.L.; Vignes, H.; Vermot, J. Mechanically activated Piezo channels modulate outflow tract valve development through the yap1 and KLF2-notch signaling axis. *eLife* **2019**, *8*, 1–27. [\[CrossRef\]](#)
40. Kang, H.; Hong, Z.; Zhong, M.; Klomp, J.; Bayless, K.J.; Mehta, D.; Karginov, A.V.; Hu, G.; Malik, A.B. Piezo1 mediates angiogenesis through activation of MT1-MMP signaling. *Am. J. Physiol.-Cell Physiol.* **2019**, *316*, C92–C103. [\[CrossRef\]](#)
41. Pathak, M.M.; Nourse, J.L.; Tran, T.; Hwe, J.; Arulmoli, J.; Le, D.T.T.; Bernardis, E.; Flanagan, L.A.; Tombola, F. Stretch-activated ion channel Piezo1 directs lineage choice in human neural stem cells. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 16148–16153. [\[CrossRef\]](#) [\[PubMed\]](#)
42. He, L.; Si, G.; Huang, J.; Samuel, A.D.; Perrimon, N. Mechanical regulation of stem-cell differentiation by the stretch-activated Piezo channel. *Nature* **2018**, *555*, 103–106. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Sun, W.; Chi, S.; Li, Y.; Ling, S.; Tan, Y.; Xu, Y.; Jiang, F.; Li, J.; Liu, C.; Zhong, G.; et al. The mechanosensitive Piezo1 channel is required for bone formation. *eLife* **2019**, *8*, 1–25. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Li, X.; Han, L.; Nookaew, I.; Mannen, E.; Silva, M.J.; Almeida, M.; Xiong, J. Stimulation of piezo1 by mechanical signals promotes bone anabolism. *eLife* **2019**, *8*, 1–22. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Song, Y.; Li, D.; Farrelly, O.; Miles, L.; Li, F.; Kim, S.E.; Lo, T.Y.; Wang, F.; Li, T.; Thompson-Peer, K.L.; et al. The Mechanosensitive Ion Channel Piezo Inhibits Axon Regeneration. *Neuron* **2019**, *102*, 373–389.e6. [\[CrossRef\]](#)
46. Solis, A.G.; Bielecki, P.; Steach, H.R.; Sharma, L.; Harman, C.C.; Yun, S.; De Zoete, M.R.; Warnock, J.N.; To, S.D.; York, A.G.; et al. Mechanosensation of cyclical force by PIEZO1 is essential for innate immunity. *Nature* **2019**, *573*, 69–74. [\[CrossRef\]](#)
47. Ma, S.; Cahalan, S.; Lamonte, G.; Grubaugh, N.D.; Zeng, W.; Murthy, S.E.; Paytas, E.; Gamini, R.; Lukacs, V.; Whitwam, T.; et al. Common PIEZO1 Allele in African Populations Causes RBC Dehydration and Attenuates Plasmodium Infection. *Cell* **2018**, *173*, 443–455.e12. [\[CrossRef\]](#)
48. Gudipaty, S.A.; Lindblom, J.; Loftus, P.D.; Redd, M.J.; Edes, K.; Davey, C.F.; Krishnegowda, V.; Rosenblatt, J. Mechanical stretch triggers rapid epithelial cell division through Piezo1. *Nature* **2017**, *543*, 118–121. [\[CrossRef\]](#)
49. Eisenhoffer, G.T.; Loftus, P.D.; Yoshigi, M.; Otsuna, H.; Chien, C.B.; Morcos, P.A.; Rosenblatt, J. Crowding induces live cell extrusion to maintain homeostatic cell numbers in epithelia. *Nature* **2012**, *484*, 546–549. [\[CrossRef\]](#)
50. Reeh, P.W.; Fischer, M.J.M. Nobel somatosensations and pain. *Pflügers Arch.-Eur. J. Physiol.* **2022**, *474*, 405–420. [\[CrossRef\]](#)
51. Lewis, A.H.; Cui, A.F.; McDonald, M.F.; Grandl, J. Transduction of Repetitive Mechanical Stimuli by Piezo1 and Piezo2 Ion Channels. *Cell Rep.* **2017**, *19*, 2572–2585. [\[CrossRef\]](#)
52. Wang, J.; La, J.H.; Hamill, O.P. PIEZO1 is selectively expressed in small diameter mouse DRG neurons distinct from neurons strongly expressing TRPV1. *Front. Mol. Neurosci.* **2019**, *12*, 1–15. [\[CrossRef\]](#)
53. Roh, J.; Hwang, S.M.; Lee, S.H.; Lee, K.; Kim, Y.H.; Park, C.K. Functional expression of piezo1 in dorsal root ganglion (DRG) neurons. *Int. J. Mol. Sci.* **2020**, *21*, 3834. [\[CrossRef\]](#)
54. Nagel, M.; Chesler, A.T. PIEZO2 ion channels in proprioception. *Curr. Opin. Neurobiol.* **2022**, *75*, 102572. [\[CrossRef\]](#)
55. Ranade, S.S.; Woo, S.H.; Dubin, A.E.; Moshourab, R.A.; Wetzel, C.; Petrus, M.; Mathur, J.; Bégay, V.; Coste, B.; Mainquist, J.; et al. Piezo2 is the major transducer of mechanical forces for touch sensation in mice. *Nature* **2014**, *516*, 121–125. [\[CrossRef\]](#)
56. Liao, D.; Hsiao, M.Y.; Xiang, G.; Zhong, P. Optimal pulse length of insonification for Piezo1 activation and intracellular calcium response. *Sci. Rep.* **2021**, *11*, 1–14. [\[CrossRef\]](#)
57. Fallon, J.B.; Macefield, V.G. Vibration sensitivity of human muscle spindles and golgi tendon organs. *Muscle Nerve* **2007**, *36*, 21–29. [\[CrossRef\]](#)

58. Handler, A.; Ginty, D.D. The mechanosensory neurons of touch and their mechanisms of activation. *Nat. Rev. Neurosci.* **2021**, *22*, 521–537. [\[CrossRef\]](#)
59. Roll, J.P.; Vedel, J.P. Kinaesthetic role of muscle afferents in man, studied by tendon vibration and microneurography. *Exp. Brain Res.* **1982**, *47*, 177–190. [\[CrossRef\]](#)
60. Roll, J.P.; Vedel, J.P.; Ribot, E. Alteration of proprioceptive messages induced by tendon vibration in man: A microneurographic study. *Exp. Brain Res.* **1989**, *76*, 213–222. [\[CrossRef\]](#)
61. Burke, D.; Hagbarth, K.E.; Löfstedt, L.; Wallin, B.G. The responses of human muscle spindle endings to vibration during isometric contraction. *J. Physiol.* **1976**, *261*, 695–711. [\[CrossRef\]](#) [\[PubMed\]](#)
62. Martin, B.J.; Park, H.S. Analysis of the tonic vibration reflex: Influence of vibration variables on motor unit synchronization and fatigue. *Eur. J. Appl. Physiol. Occup. Physiol.* **1997**, *75*, 504–511. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Seo, H.G.; Oh, B.M.; Leigh, J.H.; Chun, C.; Park, C.; Kim, C.H. Effect of Focal Muscle Vibration on Calf Muscle Spasticity: A Proof-of-Concept Study. *PMR* **2016**, *8*, 1083–1089. [\[CrossRef\]](#)
64. Maloney-Hinds, C.; Petrofsky, J.S.; Zimmerman, G.; Hessinger, D.A. The Role of Nitric Oxide in Skin Blood Flow Increases Due to Vibration in Healthy Adults and Adults with Type 2 Diabetes. *Diabetes Technol. Ther.* **2009**, *11*, 39–43. [\[CrossRef\]](#) [\[PubMed\]](#)
65. Ren, W.; Pu, F.; Luan, H.; Duan, Y.; Su, H.; Fan, Y.; Jan, Y.K. Effects of Local Vibration With Different Intermittent Durations on Skin Blood Flow Responses in Diabetic People. *Front. Bioeng. Biotechnol.* **2019**, *7*, 1–8. [\[CrossRef\]](#)
66. Liao, F.; Zhang, K.; Zhou, L.; Chen, Y.; Elliott, J.; Jan, Y. Effect of Different Local Vibration Frequencies on the Multiscale Regularity of Plantar Skin Blood Flow. *Entropy* **2020**, *22*, 1288. [\[CrossRef\]](#)
67. Zhu, X.; Wu, F.; Zhu, T.; Liao, F.; Ren, Y.; Jan, Y. Effects of Preconditioning Local Vibrations on Subsequent Plantar Skin Blood Flow Response to Walking. *Int. J. Low. Extrem. Wounds* **2021**, *20*, 143–149. [\[CrossRef\]](#)
68. Marasco, P.D.; Hebert, J.S.; Sensinger, J.W.; Shell, C.E.; Schofield, J.S.; Thumser, Z.C.; Nataraj, R.; Beckler, D.T.; Dawson, M.R.; Blustein, D.H.; et al. Illusory movement perception improves motor control for prosthetic hands. *Sci. Transl. Med.* **2018**, *10*. [\[CrossRef\]](#)
69. Goodwin, G.M.; McCloskey, D.I.; Matthews, P.B.C. The contribution of muscle afferents to kinaesthesia shown by vibration induced illusions of movement and by the effects of paralysing joint afferents. *Brain* **1972**, *95*, 705–748. [\[CrossRef\]](#)
70. Collins, D.F.; Refshauge, K.M.; Todd, G.; Gandevia, S.C. Cutaneous Receptors Contribute to Kinesthesia at the Index Finger, Elbow, and Knee. *J. Neurophysiol.* **2005**, *94*, 1699–1706. [\[CrossRef\]](#)
71. Gay, A.; Parratte, S.; Salazard, B.; Guinard, D.; Pham, T.; Légré, R.; Roll, J.P. Proprioceptive feedback enhancement induced by vibratory stimulation in complex regional pain syndrome type I: An open comparative pilot study in 11 patients. *Jt. Bone Spine* **2007**, *74*, 461–466. [\[CrossRef\]](#)
72. Hamaue, Y.; Nakano, J.; Sekino, Y.; Chuganji, S.; Sakamoto, J.; Yoshimura, T.; Okita, M.; Origuchi, T. Effects of Vibration Therapy on Immobilization-Induced Hypersensitivity in Rats. *Phys. Ther.* **2015**, *95*, 1015–1026. [\[CrossRef\]](#)
73. Rippetoe, J.; Wang, H.; James, S.A.; Dionne, C.; Block, B.; Beckner, M. Improvement of gait after 4 weeks of wearable focal muscle vibration therapy for individuals with diabetic peripheral neuropathy. *J. Clin. Med.* **2020**, *9*, 3767. [\[CrossRef\]](#)
74. Chesler, A.T.; Szczot, M.; Bharucha-Goebel, D.; Čeko, M.; Donkervoort, S.; Laubacher, C.; Hayes, L.H.; Alter, K.; Zampieri, C.; Stanley, C.; et al. The Role of PIEZO2 in Human Mechanosensation. *N. Engl. J. Med.* **2016**, *375*, 1355–1364. [\[CrossRef\]](#)
75. Coste, B.; Crest, M.; Delmas, P. Pharmacological Dissection and Distribution of Na_v1.9, T-type Ca²⁺ Currents, and Mechanically Activated Cation Currents in Different Populations of DRG Neurons. *J. Gen. Physiol.* **2007**, *129*, 57–77. [\[CrossRef\]](#)
76. Drew, L.J.; Wood, J.N.; Cesare, P. Distinct mechanosensitive properties of capsaicin-sensitive and -insensitive sensory neurons. *J. Neurosci. Off. J. Soc. Neurosci.* **2002**, *22*, 1–5. [\[CrossRef\]](#)
77. Hu, J.; Lewin, G.R. Mechanosensitive currents in the neurites of cultured mouse sensory neurones. *J. Physiol.* **2006**, *577*, 815–828. [\[CrossRef\]](#)
78. Drew, L.J.; Rohrer, D.K.; Price, M.P.; Blaver, K.E.; Cockayne, D.A.; Cesare, P.; Wood, J.N. Acid-sensing ion channels ASIC2 and ASIC3 do not contribute to mechanically activated currents in mammalian sensory neurones. *J. Physiol.* **2004**, *556*, 691–710. [\[CrossRef\]](#)
79. Drew, L.J.; Rugiero, F.; Cesare, P.; Gale, J.E.; Abrahamsen, B.; Bowden, S.; Heinzmann, S.; Robinson, M.; Brust, A.; Colless, B.; et al. High-Threshold Mechanosensitive Ion Channels Blocked by a Novel Conopeptide Mediate Pressure-Evoked Pain. *PLoS ONE* **2007**, *2*, e515. [\[CrossRef\]](#)
80. Nakamichi, R.; Ma, S.; Nonoyama, T.; Chiba, T.; Kurimoto, R.; Ohzono, H.; Olmer, M.; Shukunami, C.; Fuku, N.; Wang, G.; et al. The mechanosensitive ion channel PIEZO1 is expressed in tendons and regulates physical performance. *Sci. Transl. Med.* **2022**, *14*, eabj5557. [\[CrossRef\]](#)
81. Wetzel, C.; Hu, J.; Riethmacher, D.; Benckendorff, A.; Harder, L.; Eilers, A.; Moshourab, R.; Kozlenkov, A.; Labuz, D.; Caspani, O.; et al. A stomatin-domain protein essential for touch sensation in the mouse. *Nature* **2007**, *445*, 206–209. [\[CrossRef\]](#)
82. Moehring, F.; Halder, P.; Seal, R.P.; Stucky, C.L. Uncovering the Cells and Circuits of Touch in Normal and Pathological Settings. *Neuron* **2018**, *100*, 349–360. [\[CrossRef\]](#) [\[PubMed\]](#)

83. Stucky, C.L.; Mikesell, A.R. When soft touch hurts: How hugs become painful after spinal cord injury. In *Spinal Cord Injury Pain*; Elsevier: Amsterdam, The Netherlands, 2022; pp. 341–351. [\[CrossRef\]](#)
84. Fuchs, E. Keratins and the Skin. *Annu. Rev. Cell Dev. Biol.* **1995**, *11*, 123–154. [\[CrossRef\]](#) [\[PubMed\]](#)
85. Syeda, R.; Florendo, M.N.; Cox, C.D.; Kefauver, J.M.; Santos, J.S.; Martinac, B.; Patapoutian, A. Piezo1 Channels Are Inherently Mechanosensitive. *Cell Rep.* **2016**, *17*, 1739–1746. [\[CrossRef\]](#) [\[PubMed\]](#)
86. Li, J.; Hou, B.; Tumova, S.; Muraki, K.; Bruns, A.; Ludlow, M.J.; Sedo, A.; Hyman, A.J.; Mckeown, L.; Young, R.S.; et al. Piezo1 integration of vascular architecture with physiological force. *Nature* **2014**, *515*, 279–282. [\[CrossRef\]](#)
87. Poole, K. The Diverse Physiological Functions of Mechanically Activated Ion Channels in Mammals. *Annu. Rev. Physiol.* **2022**, *84*, 307–329. [\[CrossRef\]](#)
88. Shen, X.; Song, Z.; Xu, E.; Zhou, J.; Yan, F. Sensitization of nerve cells to ultrasound stimulation through Piezo1-targeted microbubbles. *Ultrason. Sonochem.* **2021**, *73*, 105494. [\[CrossRef\]](#)
89. Lewis, A.H.; Grandl, J. Mechanical sensitivity of Piezo1 ion channels can be tuned by cellular membrane tension. *eLife* **2015**, *4*, e12088. [\[CrossRef\]](#)
90. Poole, K.; Herget, R.; Lapatsina, L.; Ngo, H.D.; Lewin, G.R. Tuning Piezo ion channels to detect molecular-scale movements relevant for fine touch. *Nat. Commun.* **2014**, *5*, 3520. [\[CrossRef\]](#)
91. Gibbons, C.H. Basics of autonomic nervous system function. In *Clinical Neurophysiology: Basis and Technical Aspect*, 160th ed.; Levin, K.H., Chauvel, P., Eds.; Handbook of Clinical Neurology; Elsevier: Amsterdam, The Netherlands, 2019; Chapter 27, pp. 407–418. [\[CrossRef\]](#)
92. Discher, D.E.; Janmey, P.; Wang, Y.L. Tissue Cells Feel and Respond to the Stiffness of Their Substrate. *Science* **2005**, *310*, 1139–1143. [\[CrossRef\]](#)
93. Miyamoto, T.; Mochizuki, T.; Nakagomi, H.; Kira, S.; Watanabe, M.; Takayama, Y.; Suzuki, Y.; Koizumi, S.; Takeda, M.; Tominaga, M. Functional Role for Piezo1 in Stretch-evoked Ca²⁺ Influx and ATP Release in Urothelial Cell Cultures. *J. Biol. Chem.* **2014**, *289*, 16565–16575. [\[CrossRef\]](#)
94. Ridone, P.; Vassalli, M.; Martinac, B. Piezo1 mechanosensitive channels: What are they and why are they important. *Biophys. Rev.* **2019**, *11*, 795–805. [\[CrossRef\]](#)
95. Hung, W.C.; Yang, J.R.; Yankaskas, C.L.; Wong, B.S.; Wu, P.H.; Pardo-Pastor, C.; Serra, S.A.; Chiang, M.J.; Gu, Z.; Wirtz, D.; et al. Confinement Sensing and Signal Optimization via Piezo1/PKA and Myosin II Pathways. *Cell Rep.* **2016**, *15*, 1430–1441. [\[CrossRef\]](#)
96. Bartel, L.; Mosabbir, A. Possible Mechanisms for the Effects of Sound Vibration on Human Health. *Healthcare* **2021**, *9*, 597. [\[CrossRef\]](#)
97. Shibasaki, M.; Secher, N.H.; Johnson, J.M.; Crandall, C.G. Central command and the cutaneous vascular response to isometric exercise in heated humans. *J. Physiol.* **2005**, *565*, 667–673. [\[CrossRef\]](#)
98. McHugh, B.J.; Murdoch, A.; Haslett, C.; Sethi, T. Loss of the Integrin-Activating Transmembrane Protein Fam38A (Piezo1) Promotes a Switch to a Reduced Integrin-Dependent Mode of Cell Migration. *PLoS ONE* **2012**, *7*, e40346. [\[CrossRef\]](#)
99. Orsini, E.M.; Perelas, A.; Southern, B.D.; Grove, L.M.; Olman, M.A.; Scheraga, R.G. Stretching the Function of Innate Immune Cells. *Front. Immunol.* **2021**, *12*. [\[CrossRef\]](#)
100. Liang, J.; Huang, B.; Yuan, G.; Chen, Y.; Liang, F.; Zeng, H.; Zheng, S.; Cao, L.; Geng, D.; Zhou, S. Stretch-activated channel Piezo1 is up-regulated in failure heart and cardiomyocyte stimulated by AngII. *Am. J. Transl. Res.* **2017**, *9*, 2945–2955.
101. Rocio Servin-Vences, M.; Moroni, M.; Lewin, G.R.; Poole, K. Direct measurement of TRPV4 and PIEZO1 activity reveals multiple mechanotransduction pathways in chondrocytes. *eLife* **2017**, *6*. [\[CrossRef\]](#)
102. Ma, N.; Chen, D.; Lee, J.; Kuri, P.; Hernandez, E.B.; Kocan, J.; Mahmood, H.; Tichy, E.D.; Rompolas, P.; Mourkioti, F. Piezo1 regulates the regenerative capacity of skeletal muscles via orchestration of stem cell morphological states. *Sci. Adv.* **2022**, *8*, eabn0485. [\[CrossRef\]](#)
103. Liu, H.; Hu, J.; Zheng, Q.; Feng, X.; Zhan, F.; Wang, X.; Xu, G.; Hua, F. Piezo1 Channels as Force Sensors in Mechanical Force-Related Chronic Inflammation. *Front. Immunol.* **2022**, *13*, 1–20. [\[CrossRef\]](#) [\[PubMed\]](#)
104. Sugimoto, A.; Miyazaki, A.; Kawarabayashi, K.; Shono, M.; Akazawa, Y.; Hasegawa, T.; Ueda-Yamaguchi, K.; Kitamura, T.; Yoshizaki, K.; Fukumoto, S.; et al. Piezo type mechanosensitive ion channel component 1 functions as a regulator of the cell fate determination of mesenchymal stem cells. *Sci. Rep.* **2017**, *7*, 17696. [\[CrossRef\]](#) [\[PubMed\]](#)
105. Fotiou, E.; Martin-Almedina, S.; Simpson, M.A.; Lin, S.; Gordon, K.; Brice, G.; Atton, G.; Jeffery, I.; Rees, D.C.; Mignot, C.; et al. Novel mutations in PIEZO1 cause an autosomal recessive generalized lymphatic dysplasia with non-immune hydrops fetalis. *Nat. Commun.* **2015**, *6*. [\[CrossRef\]](#) [\[PubMed\]](#)

106. Li, C.; Rezaia, S.; Kammerer, S.; Sokolowski, A.; Devaney, T.; Gorischek, A.; Jahn, S.; Hackl, H.; Groschner, K.; Windpassinger, C.; et al. Piezo1 forms mechanosensitive ion channels in the human MCF-7 breast cancer cell line. *Sci. Rep.* **2015**, *5*, 8364. [[CrossRef](#)] [[PubMed](#)]
107. Albarrán-Juárez, J.; Iring, A.; Wang, S.P.; Joseph, S.; Grimm, M.; Strilic, B.; Wettschureck, N.; Althoff, T.F.; Offermanns, S. Piezo1 and Gq/G11 promote endothelial inflammation depending on flow pattern and integrin activation. *J. Exp. Med.* **2018**, *215*, 2655–2672. [[CrossRef](#)]
108. Lee, W.; Leddy, H.A.; Chen, Y.; Lee, S.H.; Zelenski, N.A.; McNulty, A.L.; Wu, J.; Beicker, K.N.; Coles, J.; Zauscher, S.; et al. Synergy between Piezo1 and Piezo2 channels confers high-strain mechanosensitivity to articular cartilage. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, E5114–E5122. [[CrossRef](#)]
109. Cahalan, S.M.; Lukacs, V.; Ranade, S.S.; Chien, S.; Bandell, M.; Patapoutian, A. Piezo1 links mechanical forces to red blood cell volume. *eLife* **2015**, *4*. [[CrossRef](#)]
110. Dampney, R.A.L.; Coleman, M.J.; Fontes, M.A.P.; Hirooka, Y.; Horiuchi, J.; Li, Y.W.; Polson, J.W.; Potts, P.D.; Tagawa, T. Central Mechanisms Underlying Short- And Long-Term Regulation Of The Cardiovascular System. *Clin. Exp. Pharmacol. Physiol.* **2002**, *29*, 261–268. [[CrossRef](#)]
111. Nourse, J.L.; Pathak, M.M. How cells channel their stress: Interplay between Piezo1 and the cytoskeleton. *Semin. Cell Dev. Biol.* **2017**, *71*, 3–12. [[CrossRef](#)]
112. Evans, E.L.; Cuthbertson, K.; Endesh, N.; Rode, B.; Blythe, N.M.; Hyman, A.J.; Hall, S.J.; Gaunt, H.J.; Ludlow, M.J.; Foster, R.; et al. Yoda1 analogue (Dooku1) which antagonizes Yoda1-evoked activation of Piezo1 and aortic relaxation. *Br. J. Pharmacol.* **2018**, *175*, 1744–1759. [[CrossRef](#)]
113. Wetzel, C.; Pifferi, S.; Picci, C.; Gök, C.; Hoffmann, D.; Bali, K.K.; Lampe, A.; Lapatsina, L.; Fleischer, R.; Smith, E.S.J.; et al. Small-molecule inhibition of STOML3 oligomerization reverses pathological mechanical hypersensitivity. *Nat. Neurosci.* **2017**, *20*, 209–218. [[CrossRef](#)]
114. Shutova, M.S.; Svitkina, T.M. Common and Specific Functions of Nonmuscle Myosin II Paralogs in Cells. *Biochemistry* **2018**, *83*, 1459–1468. [[CrossRef](#)]
115. Hyman, A.J.; Tumova, S.; Beech, D.J. Piezo1 Channels in Vascular Development and the Sensing of Shear Stress. *Curr. Top. Membr.* **2017**, *79*, 37–57. [[CrossRef](#)]
116. McHugh, B.J.; Buttery, R.; Lad, Y.; Banks, S.; Haslett, C.; Sethi, T. Integrin activation by Fam38A uses a novel mechanism of R-Ras targeting to the endoplasmic reticulum. *J. Cell Sci.* **2010**, *123*, 51–61. [[CrossRef](#)]
117. Velasco-Estevéz, M.; Rolle, S.O.; Mampay, M.; Dev, K.K.; Sheridan, G.K. Piezo1 regulates calcium oscillations and cytokine release from astrocytes. *Glia* **2020**, *68*, 145–160. [[CrossRef](#)]
118. Perko, M.J.; Nielsen, H.B.; Skak, C.; Clemmesen, J.O.; Schroeder, T.V.; Secher, N.H. Mesenteric, coeliac and splanchnic blood flow in humans during exercise. *J. Physiol.* **1998**, *513*, 907–913. [[CrossRef](#)]
119. Qamar, M.I.; Read, A.E. Effects of exercise on mesenteric blood flow in man. *Gut* **1987**, *28*, 583–587. [[CrossRef](#)]
120. Thijssen, D.H.J.; Dawson, E.A.; Black, M.A.; Hopman, M.T.E.; Cable, N.T.; Green, D.J. Brachial artery blood flow responses to different modalities of lower limb exercise. *Med. Sci. Sport. Exerc.* **2009**, *41*, 1072–1079. [[CrossRef](#)]
121. Joyner, M.J.; Casey, D.P. Regulation of increased blood flow (Hyperemia) to muscles during exercise: A hierarchy of competing physiological needs. *Physiol. Rev.* **2015**, *95*, 549–601. [[CrossRef](#)]
122. Clifford, P.S. Skeletal muscle vasodilatation at the onset of exercise. *J. Physiol.* **2007**, *583*, 825–833. [[CrossRef](#)]
123. Holwerda, S.W.; Restaino, R.M.; Fadel, P.J. Adrenergic and non-adrenergic control of active skeletal muscle blood flow: Implications for blood pressure regulation during exercise. *Auton. Neurosci. Basic Clin.* **2015**, *188*, 24–31. [[CrossRef](#)] [[PubMed](#)]
124. Brown, M.D.; Hudlicka, O. Modulation of physiological angiogenesis in skeletal muscle by mechanical forces: Involvement of VEGF and metalloproteinases. *Angiogenesis* **2003**, *6*, 1–14. [[CrossRef](#)] [[PubMed](#)]
125. García-Mesa, Y.; García-Piqueras, J.; García, B.; Feito, J.; Cabo, R.; Cobo, J.; Vega, J.A.; García-Suárez, O. Merkel cells and Meissner's corpuscles in human digital skin display Piezo2 immunoreactivity. *J. Anat.* **2017**, *231*, 978–989. [[CrossRef](#)] [[PubMed](#)]
126. García-Piqueras, J.; García-Mesa, Y.; Cárcaba, L.; Feito, J.; Torres-Parejo, I.; Martín-Biedma, B.; Cobo, J.; García-Suárez, O.; Vega, J.A. Ageing of the somatosensory system at the periphery: Age-related changes in cutaneous mechanoreceptors. *J. Anat.* **2019**, *234*, 839–852. [[CrossRef](#)] [[PubMed](#)]
127. Woo, S.H.; Ranade, S.; Weyer, A.D.; Dubin, A.E.; Baba, Y.; Qiu, Z.; Petrus, M.; Miyamoto, T.; Reddy, K.; Lumpkin, E.A.; et al. Piezo2 is required for Merkel-cell mechanotransduction. *Nature* **2014**, *509*, 622–626. [[CrossRef](#)]
128. Ikeda, R.; Cha, M.; Ling, J.; Jia, Z.; Coyle, D.; Gu, J.G. Merkel cells transduce and encode tactile stimuli to drive A β -afferent impulses. *Cell* **2014**, *157*, 664–675. [[CrossRef](#)]
129. Maksimovic, S.; Nakatani, M.; Baba, Y.; Nelson, A.M.; Marshall, K.L.; Wellnitz, S.A.; Firozi, P.; Woo, S.H.; Ranade, S.; Patapoutian, A.; et al. Epidermal Merkel cells are mechanosensory cells that tune mammalian touch receptors. *Nature* **2014**, *509*, 617–621. [[CrossRef](#)]

130. Woo, S.H.; Lukacs, V.; De Nooij, J.C.; Zaytseva, D.; Criddle, C.R.; Francisco, A.G.; Jessell, T.M.; Wilkinson, K.A.; Patapoutian, A. Piezo2 is the principal mechanotransduction channel for proprioception. *Nat. Neurosci.* **2015**, *18*, 1756–1762. [[CrossRef](#)]
131. Ernfors, P.; Manira, A.E.; Svenningsson, P. *Discoveries of Receptors for Temperature and Touch*; The Noble Assembly at Karolinska Institutet: Stockholm, Sweden, 2021; pp. 2–5.
132. Von Buchholtz, L.J.; Ghitani, N.; Lam, R.M.; Licholai, J.A.; Chesler, A.T.; Ryba, N.J. Decoding Cellular Mechanisms for Mechanosensory Discrimination. *Neuron* **2021**, *109*, 285–298.e5. [[CrossRef](#)]
133. Florez-Paz, D.; Bali, K.K.; Kuner, R.; Gomis, A. A critical role for Piezo2 channels in the mechanotransduction of mouse proprioceptive neurons. *Sci. Rep.* **2016**, *6*, 1–9. [[CrossRef](#)]
134. Yang, H.; Liu, C.; Zhou, R.M.; Yao, J.; Li, X.M.; Shen, Y.; Cheng, H.; Yuan, J.; Yan, B.; Jiang, Q. Piezo2 protein: A novel regulator of tumor angiogenesis and hyperpermeability. *Oncotarget* **2016**, *7*, 44630–44643. [[CrossRef](#)]
135. Nonomura, K.; Woo, S.H.; Chang, R.B.; Gillich, A.; Qiu, Z.; Francisco, A.G.; Ranade, S.S.; Liberles, S.D.; Patapoutian, A. Piezo2 senses airway stretch and mediates lung inflation-induced apnoea. *Nature* **2017**, *541*, 176–181. [[CrossRef](#)]
136. Ferrari, L.F.; Bogen, O.; Green, P.; Levine, J.D. Contribution of Piezo2 to endothelium-dependent pain. *Mol. Pain* **2015**, *11*, 1–8. [[CrossRef](#)]
137. Case, L.K.; Liljencrantz, J.; Madian, N.; Necaie, A.; Tubbs, J.; McCall, M.; Bradson, M.L.; Szczot, M.; Pitcher, M.H.; Ghitani, N.; et al. Innocuous pressure sensation requires A-type afferents but not functional PIEZO2 channels in humans. *Nat. Commun.* **2021**, *12*. [[CrossRef](#)]
138. Nagi, S.S.; Marshall, A.G.; Makdani, A.; Jarocka, E.; Liljencrantz, J.; Ridderström, M.; Shaikh, S.; O'Neill, F.; Saade, D.; Donkervoort, S.; et al. An ultrafast system for signaling mechanical pain in human skin. *Sci. Adv.* **2019**, *5*. [[CrossRef](#)]
139. Bevan, S.; Quallo, T.; Andersson, D.A. TRPV1. In *Handbook of Experimental Pharmacology*, 222th ed.; Springer: Berlin/Heidelberg, Germany, 2014; pp. 207–245. [[CrossRef](#)]
140. Moriello, A.S.; De Petrocellis, L. Assay of TRPV1 Receptor Signaling. In *Methods in Molecular Biology*, 1412th ed.; Springer: New York, NY, USA, 2016; pp. 65–76. [[CrossRef](#)]
141. Storozhuk, M.V.; Moroz, O.F.; Zholos, A.V. Multifunctional TRPV1 Ion Channels in Physiology and Pathology with Focus on the Brain, Vasculature, and Some Visceral Systems. *BioMed Res. Int.* **2019**, *2019*. [[CrossRef](#)]
142. Ben-Shahar, Y. Sensory Functions for Degenerin/Epithelial Sodium Channels (DEG/ENaC). In *Advances in Genetics*, 76th ed.; Academic Press: Cambridge, MA, USA, 2011; Chapter 1, pp. 1–26. [[CrossRef](#)]
143. Lin, S.H.; Cheng, Y.R.; Banks, R.W.; Min, M.Y.; Bewick, G.S.; Chen, C.C. Evidence for the involvement of ASIC3 in sensory mechanotransduction in proprioceptors. *Nat. Commun.* **2016**, *7*, 11460. [[CrossRef](#)]
144. Perozo, E.; Kloda, A.; Cortes, D.M.; Martinac, B. Physical principles underlying the transduction of bilayer deformation forces during mechanosensitive channel gating. *Nat. Struct. Biol.* **2002**, *9*, 696–703. [[CrossRef](#)]
145. Nomura, T.; Cranfield, C.G.; Deplazes, E.; Owen, D.M.; Macmillan, A.; Battle, A.R.; Constantine, M.; Sokabe, M.; Martinac, B. Differential effects of lipids and lyso-lipids on the mechanosensitivity of the mechanosensitive channels MscL and MscS. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 8770–8775. [[CrossRef](#)]
146. Brohawn, S.G.; Su, Z.; Mackinnon, R. Mechanosensitivity is mediated directly by the lipid membrane in TRAAK and TREK1 K⁺ channels. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 3614–3619. [[CrossRef](#)]
147. Murthy, S.E.; Dubin, A.E.; Whitwam, T.; Jojoa-Cruz, S.; Cahalan, S.M.; Mousavi, S.A.R.; Ward, A.B.; Patapoutian, A. OSCA/TMEM63 are an evolutionarily conserved family of mechanically activated ion channels. *eLife* **2018**, *7*, e41844. [[CrossRef](#)] [[PubMed](#)]
148. Zhang, M.J.; Yin, Y.W.; Li, B.H.; Liu, Y.; Liao, S.Q.; Gao, C.Y.; Li, J.C.; Zhang, L.L. The role of TRPV1 in improving VSMC function and attenuating hypertension. *Prog. Biophys. Mol. Biol.* **2015**, *117*, 212–216. [[CrossRef](#)] [[PubMed](#)]
149. Baylie, R.L.; Brayden, J.E. TRPV channels and vascular function. *Acta Physiol.* **2011**, *203*, 99–116. [[CrossRef](#)] [[PubMed](#)]
150. Yang, D.; Luo, Z.; Ma, S.; Wong, W.T.; Ma, L.; Zhong, J.; He, H.; Zhao, Z.; Cao, T.; Yan, Z.; et al. Activation of TRPV1 by Dietary Capsaicin Improves Endothelium-Dependent Vasorelaxation and Prevents Hypertension. *Cell Metab.* **2010**, *12*, 130–141. [[CrossRef](#)] [[PubMed](#)]
151. Choi, S.; Lim, J.Y.; Yoo, S.; Kim, H.; Hwang, S.W. Emerging Role of Spinal Cord TRPV1 in Pain Exacerbation. *Neural Plast.* **2016**, *2016*, 1–10. [[CrossRef](#)]
152. Yang, S.; Yang, F.; Wei, N.; Hong, J.; Li, B.; Luo, L.; Rong, M.; Yarov-Yarovoy, V.; Zheng, J.; Wang, K.; et al. A pain-inducing centipede toxin targets the heat activation machinery of nociceptor TRPV1. *Nat. Commun.* **2015**, *6*, 8297. [[CrossRef](#)]
153. Szallasi, A.; Cortright, D.N.; Blum, C.A.; Eid, S.R. The vanilloid receptor TRPV1: 10 years from channel cloning to antagonist proof-of-concept. *Nat. Rev. Drug Discov.* **2007**, *6*, 357–372. [[CrossRef](#)]
154. Woolums, B.M.; Mccray, B.A.; Sung, H.; Tabuchi, M.; Sullivan, J.M.; Ruppell, K.T.; Yang, Y.; Mamah, C.; Aisenberg, W.H.; Saavedra-Rivera, P.C.; et al. TRPV4 disrupts mitochondrial transport and causes axonal degeneration via a CaMKII-dependent elevation of intracellular Ca²⁺. *Nat. Commun.* **2020**, *11*, 1–17. [[CrossRef](#)]

155. Phan, T.X.; Ton, H.T.; Gulyás, H.; Pórszász, R.; Tóth, A.; Russo, R.; Kay, M.W.; Sahibzada, N.; Ahern, G.P. TRPV1 expressed throughout the arterial circulation regulates vasoconstriction and blood pressure. *J. Physiol.* **2020**, *598*, 5639–5659. [\[CrossRef\]](#)
156. Christie, S.; Wittert, G.A.; Li, H.; Page, A.J. Involvement of TRPV1 Channels in Energy Homeostasis. *Front. Endocrinol.* **2018**, *9*, 420. [\[CrossRef\]](#)
157. Amantini, C.; Farfariello, V.; Cardinali, C.; Morelli, M.B.; Marinelli, O.; Nabissi, M.; Santoni, M.; Bonfili, L.; Cecarini, V.; Eleuteri, A.M.; et al. The TRPV1 ion channel regulates thymocyte differentiation by modulating autophagy and proteasome activity. *Oncotarget* **2017**, *8*, 90766–90780. [\[CrossRef\]](#)
158. Li, Y.; Gupta, P. Immune aspects of the bi-directional neuroimmune facilitator TRPV1. *Mol. Biol. Rep.* **2019**, *46*, 1499–1510. [\[CrossRef\]](#)
159. Lee, E.; Jung, D.Y.; Kim, J.H.; Patel, P.R.; Hu, X.; Lee, Y.; Azuma, Y.; Wang, H.; Tsitsilianos, N.; Shafiq, U.; et al. Transient receptor potential vanilloid type-1 channel regulates diet-induced obesity, insulin resistance, and leptin resistance. *FASEB J.* **2015**, *29*, 3182–3192. [\[CrossRef\]](#)
160. Mistretta, F.; Buffi, N.M.; Lughezzani, G.; Lista, G.; Larcher, A.; Fossati, N.; Abrate, A.; Dell'Oglio, P.; Montorsi, F.; Guazzoni, G.; et al. Bladder Cancer and Urothelial Impairment: The Role of TRPV1 as Potential Drug Target. *BioMed Res. Int.* **2014**, *2014*, 1–10. [\[CrossRef\]](#)
161. Sterle, I.; Zupančič, D.; Romih, R. Correlation between Urothelial Differentiation and Sensory Proteins P2X3, P2X5, TRPV1, and TRPV4 in Normal Urothelium and Papillary Carcinoma of Human Bladder. *BioMed Res. Int.* **2014**, *2014*, 1–9. [\[CrossRef\]](#)
162. McGarvey, L.P.; Butler, C.A.; Stokesberry, S.; Polley, L.; Mcquaid, S.; Abdullah, H.; Ashraf, S.; McGahon, M.K.; Curtis, T.M.; Arron, J.; et al. Increased expression of bronchial epithelial transient receptor potential vanilloid 1 channels in patients with severe asthma. *J. Allergy Clin. Immunol.* **2014**, *133*, 704–712.e4. [\[CrossRef\]](#)
163. Feng, J.; Yang, P.; Mack, M.R.; Dryn, D.; Luo, J.; Gong, X.; Liu, S.; Oetjen, L.K.; Zholos, A.V.; Mei, Z.; et al. Sensory TRP channels contribute differentially to skin inflammation and persistent itch. *Nat. Commun.* **2017**, *8*, 980. [\[CrossRef\]](#)
164. Bai, L.; Lehnert, B.P.; Liu, J.; Neubarth, N.L.; Dickendesher, T.L.; Nwe, P.H.; Cassidy, C.; Woodbury, C.J.; Ginty, D.D. Genetic Identification of an Expansive Mechanoreceptor Sensitive to Skin Stroking. *Cell* **2015**, *163*, 1783–1795. [\[CrossRef\]](#)
165. Neubarth, N.L.; Emanuel, A.J.; Liu, Y.; Springel, M.W.; Handler, A.; Zhang, Q.; Lehnert, B.P.; Guo, C.; Orefice, L.L.; Abdelaziz, A.; et al. Meissner corpuscles and their spatially intermingled afferents underlie gentle touch perception. *Science* **2020**, *368*, eabb2751. [\[CrossRef\]](#)
166. Lewin, G.R.; McMahon, S.B. Physiological properties of primary sensory neurons appropriately and inappropriately innervating skin in the adult rat. *J. Neurophysiol.* **1991**, *66*, 1205–1217. [\[CrossRef\]](#)
167. Koltzenburg, M.; Stucky, C.L.; Lewin, G.R. Receptive properties of mouse sensory neurons innervating hairy skin. *J. Neurophysiol.* **1997**, *78*, 1841–1850. [\[CrossRef\]](#) [\[PubMed\]](#)
168. Johansson, R.S.; Vallbo, Å.B.; Westling, G. Thresholds of mechanosensitive afferents in the human hand as measured with von Frey hairs. *Brain Res.* **1980**, *184*, 343–351. [\[CrossRef\]](#) [\[PubMed\]](#)
169. Cain, D.M.; Khasabov, S.G.; Simone, D.A. Response properties of mechanoreceptors and nociceptors in mouse glabrous skin: An in vivo study. *J. Neurophysiol.* **2001**, *85*, 1561–1574. [\[CrossRef\]](#) [\[PubMed\]](#)
170. Li, L.; Rutlin, M.; Abaira, V.E.; Cassidy, C.; Kus, L.; Gong, S.; Jankowski, M.P.; Luo, W.; Heintz, N.; Koerber, H.R.; et al. The functional organization of cutaneous low-threshold mechanosensory neurons. *Cell* **2011**, *147*, 1615–1627. [\[CrossRef\]](#) [\[PubMed\]](#)
171. Mauguière, F.; Merlet, I.; Forss, N.; Vanni, S.; Jousmäki, V.; Adeleine, P.; Hari, R. Activation of a distributed somatosensory cortical network in the human brain: A dipole modelling study of magnetic fields evoked by median nerve stimulation. Part II: Effects of stimulus rate, attention and stimulus detection. *Electroencephalogr. Clin. Neurophysiol. Potentials Sect.* **1997**, *104*, 290–295. [\[CrossRef\]](#)
172. Mauguière, F.; Merlet, I.; Forss, N.; Vanni, S.; Jousmäki, V.; Adeleine, P.; Hari, R. Activation of a distributed somatosensory cortical network in the human brain. A dipole modelling study of magnetic fields evoked by median nerve stimulation. Part I: Location and activation timing of SEF sources. *Electroencephalogr. Clin. Neurophysiol. Potentials Sect.* **1997**, *104*, 281–289. [\[CrossRef\]](#)
173. Ackerley, R.; Kavounoudias, A. The role of tactile afference in shaping motor behaviour and implications for prosthetic innovation. *Neuropsychologia* **2015**, *79*, 192–205. [\[CrossRef\]](#)
174. Perl, E.R. Myelinated afferent fibres innervating the primate skin and their response to noxious stimuli. *J. Physiol.* **1968**, *197*, 593–615. [\[CrossRef\]](#)
175. Burgess, P.R.; Petit, D.; Warren, R.M. Receptor types in cat hairy skin supplied by myelinated fibers. *J. Neurophysiol.* **1968**, *31*, 833–848. [\[CrossRef\]](#)
176. Brown, A.G.; Iggo, A. A quantitative study of cutaneous receptors and afferent fibres in the cat and rabbit. *J. Physiol.* **1967**, *193*, 707–733. [\[CrossRef\]](#)
177. Knibestöl, M. Stimulus–response functions of rapidly adapting mechanoreceptors in the human glabrous skin area. *J. Physiol.* **1973**, *232*, 427–452. [\[CrossRef\]](#)
178. Leem, J.W.; Willis, W.D.; Chung, J.M. Cutaneous sensory receptors in the rat foot. *J. Neurophysiol.* **1993**, *69*, 1684–1699. [\[CrossRef\]](#)
179. Zimmerman, A.; Bai, L.; Ginty, D.D. The gentle touch receptors of mammalian skin. *Science* **2014**, *346*, 950–954. [\[CrossRef\]](#)

180. Bardouille, T.; Picton, T.W.; Ross, B. Attention modulates beta oscillations during prolonged tactile stimulation. *Eur. J. Neurosci.* **2010**, *31*, 761–769. [[CrossRef](#)]
181. Melzack, R.; Wall, P.D. Pain Mechanisms: A New Theory. *Science* **1965**, *150*, 971–979. [[CrossRef](#)]
182. Danilov, Y.P. Translingual Neurostimulation (TLNS): A novel approach to neurorehabilitation. *J. Neurol. Neurophysiol.* **2017**, *8*. [[CrossRef](#)]
183. De Cicco, V.; Tramonti Fantozzi, M.P.; Cataldo, E.; Barresi, M.; Bruschini, L.; Faraguna, U.; Manzoni, D. Trigeminal, Visceral and Vestibular Inputs May Improve Cognitive Functions by Acting through the Locus Coeruleus and the Ascending Reticular Activating System: A New Hypothesis. *Front. Neuroanat.* **2018**, *11*. [[CrossRef](#)]
184. Gillespie, P.G.; Walker, R.G. Molecular basis of mechanosensory transduction. *Nature* **2001**, *413*, 194–202. [[CrossRef](#)]
185. McGlone, F.; Reilly, D. The cutaneous sensory system. *Neurosci. Biobehav. Rev.* **2010**, *34*, 148–159. [[CrossRef](#)]
186. Rice, F.L.; Albrecht, P.J. Cutaneous Mechanisms of Tactile Perception: Morphological and Chemical Organization of the Innervation to the Skin. *Senses: A Compr. Ref.* **2008**, *6*, 1–31. [[CrossRef](#)]
187. Cobo, R.; García-Piqueras, J.; Cobo, J.; Vega, J.A. The human cutaneous sensory corpuscles: An update. *J. Clin. Med.* **2021**, *10*, 227. [[CrossRef](#)] [[PubMed](#)]
188. Munger, L.B.; Ide, C. The Structure and Function of Cutaneous Sensory Receptors. *Arch. Histol. Cytol.* **1988**, *51*, 1–34. [[CrossRef](#)] [[PubMed](#)]
189. Zelená, J. *Nerves and Mechanoreceptors: The Role of Innervation in the Development and Maintenance of Mammalian Mechanoreceptors*; Chapman & Hall: London, UK, 1994.
190. Gardner, E.P.; Martin, J.H.; Jessell, T.M. Coding of sensory information. In *Principles of Neural Science*; Kandel, E.R., Schwartz, J.H., Jessell, T.M., Eds.; Oxford University Press: New York, NY, USA, 2000; Chapter 21, pp. 430–449.
191. Strzalkowski, N.D.J.; Peters, R.M.; Inglis, J.T.; Bent, L.R. Cutaneous afferent innervation of the human foot sole: What can we learn from single-unit recordings? *J. Neurophysiol.* **2018**, *120*, 1233–1246. [[CrossRef](#)] [[PubMed](#)]
192. Vallbo, Å.B.; Olsson, H.; Wessberg, J.; Norrsköld, U. A system of unmyelinated afferents for innocuous mechanoreception in the human skin. *Brain Res.* **1993**, *628*, 301–304. [[CrossRef](#)]
193. Vallbo, Å.B.; Olsson, H.; Wessberg, J.; Kakuda, N. Receptive field characteristics of tactile units with myelinated afferents in hairy skin of human subjects. *J. Physiol.* **1995**, *483*, 783–795. [[CrossRef](#)]
194. Vallbo, Å.B.; Olsson, H.; Wessberg, J. Unmyelinated afferents constitute a second system coding tactile stimuli of the human hairy skin. *J. Neurophysiol.* **1999**, *81*, 2753–2763. [[CrossRef](#)]
195. Seal, R.P.; Wang, X.; Guan, Y.; Raja, S.N.; Woodbury, C.J.; Basbaum, A.I.; Edwards, R.H. Injury-induced mechanical hypersensitivity requires C-low threshold mechanoreceptors. *Nature* **2009**, *462*, 651–655. [[CrossRef](#)]
196. Abdo, H.; Calvo-Enrique, L.; Lopez, J.M.; Song, J.; Zhang, M.D.; Usoskin, D.; Manira, A.E.; Adameyko, I.; Hjerling-Leffler, J.; Ernfors, P. Specialized cutaneous schwann cells initiate pain sensation. *Science* **2019**, *365*, 695–699. [[CrossRef](#)]
197. Hoffman, B.U.; Baba, Y.; Griffith, T.N.; Mosharov, E.V.; Woo, S.H.; Roybal, D.D.; Karsenty, G.; Patapoutian, A.; Sulzer, D.; Lumpkin, E.A. Merkel Cells Activate Sensory Neural Pathways through Adrenergic Synapses. *Neuron* **2018**, *100*, 1401–1413.e6. [[CrossRef](#)]
198. Schwaller, F.; Bégy, V.; García-García, G.; Taberner, F.J.; Moshourab, R.; McDonald, B.; Docter, T.; Kühnemund, J.; Ojeda-Alonso, J.; Paricio-Montesinos, R.; et al. USH2A is a Meissner's corpuscle protein necessary for normal vibration sensing in mice and humans. *Nat. Neurosci.* **2021**, *24*, 74–81. [[CrossRef](#)]
199. Caterina, M.J.; Schumacher, M.A.; Tominaga, M.; Rosen, T.A.; Levine, J.D.; Julius, D. The capsaicin receptor: A heat-activated ion channel in the pain pathway. *Nature* **1997**, *389*, 816–824. [[CrossRef](#)]
200. McKemy, D.D.; Neuhauser, W.M.; Julius, D. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. *Nature* **2002**, *416*, 52–58. [[CrossRef](#)]
201. Güler, A.D.; Lee, H.; Iida, T.; Shimizu, I.; Tominaga, M.; Caterina, M. Heat-Evoked Activation of the Ion Channel, TRPV4. *J. Neurosci.* **2002**, *22*, 6408–6414. [[CrossRef](#)]
202. Talagas, M.; Lebonvallet, N.; Berthod, F.; Misery, L. Lifting the veil on the keratinocyte contribution to cutaneous nociception. *Protein Cell* **2020**, *11*, 239–250. [[CrossRef](#)]
203. Sadler, K.E.; Moehring, F.; Stucky, C.L. Keratinocytes contribute to normal cold and heat sensation. *eLife* **2020**, *9*, 1–14. [[CrossRef](#)]
204. Chung, M.K.; Lee, H.; Mizuno, A.; Suzuki, M.; Caterina, M.J. TRPV3 and TRPV4 mediate warmth-evoked currents in primary mouse keratinocytes. *J. Biol. Chem.* **2004**, *279*, 21569–21575. [[CrossRef](#)]
205. Moehring, F.; Cowie, A.M.; Menzel, A.D.; Weyer, A.D.; Grzybowski, M.; Arzua, T.; Geurts, A.M.; Palygin, O.; Stucky, C.L. Keratinocytes mediate innocuous and noxious touch via ATP-P2X4 signaling. *eLife* **2018**, *7*, 1–35. [[CrossRef](#)]
206. Abaira, V.E.; Ginty, D.D. The sensory neurons of touch. *Neuron* **2013**, *79*, 618–639. [[CrossRef](#)]
207. Marshall, K.; Patapoutian, A. Getting a grip on touch receptors. *Science* **2020**, *368*, 1311–1312. . 7610. [[CrossRef](#)]
208. Delmas, P.; Hao, J.; Rodat-Despoix, L. Molecular mechanisms of mechanotransduction in mammalian sensory neurons. *Nat. Rev. Neurosci.* **2011**, *12*, 139–153. [[CrossRef](#)]

209. Fleming, M.S.; Luo, W. The anatomy, function, and development of mammalian A β low-threshold mechanoreceptors. *Front. Biol.* **2013**, *8*, 408–420. [[CrossRef](#)] [[PubMed](#)]
210. Olson, W.; Dong, P.; Fleming, M.; Luo, W. The specification and wiring of mammalian cutaneous low-threshold mechanoreceptors. *Wiley Interdiscip. Rev. Dev. Biol.* **2016**, *5*, 389–404. [[CrossRef](#)] [[PubMed](#)]
211. Coleman, G.T.; Bahramali, H.; Zhang, H.Q.; Rowe, M.J. Characterization of Tactile Afferent Fibers in the Hand of the Marmoset Monkey. *J. Neurophysiol.* **2001**, *85*, 1793–1804. [[CrossRef](#)] [[PubMed](#)]
212. Tzen, Y.T.; Weinheimer-Haus, E.M.; Corbiere, T.F.; Koh, T.J. Increased skin blood flow during low intensity vibration in human participants: Analysis of control mechanisms using short-time fourier transform. *PLoS ONE* **2018**, *13*, e0200247. [[CrossRef](#)] [[PubMed](#)]
213. Krajnak, K.; Dong, R.G.; Flavahan, S.; Welcome, D.; Flavahan, N.A. Acute vibration increases α 2C-adrenergic smooth muscle constriction and alters thermosensitivity of cutaneous arteries. *J. Appl. Physiol.* **2006**, *100*, 1230–1237. [[CrossRef](#)]
214. Krajnak, K.; Miller, G.R.; Waugh, S.; Johnson, C.; Kashon, M.L. Characterization of frequency-dependent responses of the vascular system to repetitive vibration. *J. Occup. Environ. Med.* **2012**, *54*, 1010–1016. [[CrossRef](#)]
215. Bovenzi, M.; Lindsell, C.J.; Griffin, M.J. Magnitude of acute exposures to vibration and finger circulation. *Scand. J. Work. Environ. Health* **1999**, *25*, 278–284. [[CrossRef](#)]
216. Souron, R.; Besson, T.; Millet, G.Y.; Lapole, T. Acute and chronic neuromuscular adaptations to local vibration training. *Eur. J. Appl. Physiol.* **2017**, *117*, 1939–1964. [[CrossRef](#)]
217. Salter, M.W.; Henry, J.L. Evidence that adenosine mediates the depression of spinal dorsal horn neurons induced by peripheral vibration in the cat. *Neuroscience* **1987**, *22*, 631–650. [[CrossRef](#)]
218. Naghdi, L.; Ahonen, H.; Macario, P.; Bartel, L. The effect of low-frequency sound stimulation on patients with fibromyalgia: A clinical study. *Pain Res. Manag.* **2015**, *20*, e21–e27. [[CrossRef](#)]
219. Serritella, E.; Scialanca, G.; Di Giacomo, P.; Di Paolo, C. Local Vibratory Stimulation for Temporomandibular Disorder Myofascial Pain Treatment: A Randomised, Double-Blind, Placebo-Controlled Preliminary Study. *Pain Res. Manag.* **2020**, *2020*. [[CrossRef](#)]
220. Chen, L.; Feng, Y.; Chen, B.; Wang, Q.; Wei, K. Improving postural stability among people with lower-limb amputations by tactile sensory substitution. *J. NeuroEngineering Rehabil.* **2021**, *18*, 1–14. [[CrossRef](#)]
221. Steyvers, M.; Levin, O.; Verschuere, S.M.; Swinnen, S.P. Frequency-dependent effects of muscle tendon vibration on corticospinal excitability: A TMS study. *Exp. Brain Res.* **2003**, *151*, 9–14. [[CrossRef](#)]
222. Kawahira, K.; Higashihara, K.; Matsumoto, S.; Shimodozono, M.; Etoh, S.; Tanaka, N.; Sueyoshi, Y. New functional vibratory stimulation device for extremities in patients with stroke. *Int. J. Rehabil. Res.* **2004**, *27*, 335–337. [[CrossRef](#)]
223. Chandrashekar, R.; Wang, H.; Dionne, C.; James, S.; Burzycki, J. Wearable focal muscle vibration on pain, balance, mobility, and sensation in individuals with diabetic peripheral neuropathy: A pilot study. *Int. J. Environ. Res. Public Health* **2021**, *18*, 2415. [[CrossRef](#)]
224. Koike, Y.; Iwamoto, S.; Kimata, Y.; Nohno, T.; Hiragami, F.; Kawamura, K.; Numata, K.; Murai, H.; Okisima, K.; Iwata, M.; et al. Low-Frequency Vibratory Sound Induces Neurite Outgrowth In PC12M3 Cells In Which Nerve Growth Factor-Induced Neurite Outgrowth Is Impaired. *Tissue Cult. Res. Commun.* **2004**, *23*, 81–90. [[CrossRef](#)]
225. Koike, Y.; Tutida, R.; Hayashi, Y.; Yamanishi, Y.; Kano, Y. Low-Frequency, Whole Body Vibration Induced Neurite Outgrowth by Pc12m3 Cells with Impaired Nerve Growth Factor-Induced Neurite Outgrowth. *J. Nov. Physiother.* **2015**, *05*, 1–5. [[CrossRef](#)]
226. Barralon, P.; Dumont, G.; Schwarz, S.K.; Ansermino, J.M. Autonomic nervous system response to vibrating and electrical stimuli on the forearm and wrist. In Proceedings of the 2008 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Vancouver, BC, Canada, 20–25 August 2008; pp. 931–934. [[CrossRef](#)]
227. Chambers, M.R.; Andres, K.H.; Duering, M.V.; Iggo, A. The structure and function of the slowly adapting type II mechanoreceptor in hairy skin. *Q. J. Exp. Physiol. Cogn. Med. Sci.* **1972**, *57*, 417–445. [[CrossRef](#)]
228. Johansson, R.S.; Vallbo, A.B. Tactile sensibility in the human hand: Relative and absolute densities of four types of mechanoreceptive units in glabrous skin. *J. Physiol.* **1979**, *286*, 283–300. [[CrossRef](#)]
229. Paré, M.; Smith, A.M.; Rice, F.L. Distribution and terminal arborizations of cutaneous mechanoreceptors in the glabrous finger pads of the monkey. *J. Comp. Neurol.* **2002**, *445*, 347–359. [[CrossRef](#)]
230. Torebjörk, H.E.; Hallin, R.G. Perceptual changes accompanying controlled preferential blocking of A and C fibre responses in intact human skin nerves. *Exp. Brain Res.* **1973**, *16*, 321–332. [[CrossRef](#)] [[PubMed](#)]
231. Mackenzie, R.A.; Burke, D.; Skuse, N.F.; Lethlean, A.K. Fibre function and perception during cutaneous nerve block. *J. Neurol. Neurosurg. Psychiatry* **1975**, *38*, 865–873. [[CrossRef](#)] [[PubMed](#)]
232. Ochoa, J.; Torebjörk, E. Sensations evoked by intraneural microstimulation of C nociceptor fibres in human skin nerves. *J. Physiol.* **1989**, *415*, 583–599. [[CrossRef](#)] [[PubMed](#)]
233. Bromm, B.; Treede, R.D. Nerve fibre discharges, cerebral potentials and sensations induced by CO₂ laser stimulation. *Hum. Neurobiol.* **1984**, *3*, 33–40.
234. Löken, L.S.; Wessberg, J.; Morrison, I.; McGlone, F.; Olsson, H. Coding of pleasant touch by unmyelinated afferents in humans. *Nat. Neurosci.* **2009**, *12*, 547–548. [[CrossRef](#)]

235. Kuiken, T.A.; Marasco, P.D.; Lock, B.A.; Harden, R.N.; Dewald, J.P.A. Redirection of cutaneous sensation from the hand to the chest skin of human amputees with targeted reinnervation. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 20061–20066. [\[CrossRef\]](#)
236. Melzack, R. Pain and the Neuromatrix in the Brain. *J. Dent. Educ.* **2001**, *65*, 1378–1382. [\[CrossRef\]](#)
237. Moayed, M.; Davis, K.D. Theories of pain: From specificity to gate control. *J. Neurophysiol.* **2013**, *109*, 5–12. [\[CrossRef\]](#)
238. Guyenet, P.G. Regulation of breathing and autonomic outflows by chemoreceptors. *Compr. Physiol.* **2014**, *4*, 1511–1562. [\[CrossRef\]](#)
239. Yuan, H.; Silberstein, S.D. Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review: Part I. *Headache J. Head Face Pain* **2016**, *56*, 71–78. [\[CrossRef\]](#)
240. Darrow, M.J.; Mian, T.M.; Torres, M.; Haider, Z.; Danaphongse, T.; Seyedahmadi, A.; Rennaker, R.L.; Hays, S.A.; Kilgard, M.P. The tactile experience paired with vagus nerve stimulation determines the degree of sensory recovery after chronic nerve damage. *Behav. Brain Res.* **2021**, *396*, 112910. [\[CrossRef\]](#)
241. Baig, S.S.; Kamarova, M.; Ali, A.; Su, L.; Dawson, J.; Redgrave, J.N.; Majid, A. Transcutaneous vagus nerve stimulation (tVNS) in stroke: The evidence, challenges and future directions. *Auton. Neurosci. Basic Clin.* **2022**, *237*. [\[CrossRef\]](#)
242. Moggi, L.; De Sire, A.; Marotta, N.; Demeco, A.; Ammendolia, A. Vibration therapy role in neurological diseases rehabilitation: An umbrella review of systematic reviews. *Disabil. Rehabil.* **2021**, *1–9*. [\[CrossRef\]](#)
243. Flor, H.; Denke, C.; Schaefer, M.; Grüsser, S. Effect of sensory discrimination training on cortical reorganisation and phantom limb pain. *Lancet* **2001**, *357*, 1763–1764. [\[CrossRef\]](#)
244. Flor, H.; Diers, M.; Andoh, J. The neural basis of phantom limb pain. *Trends Cogn. Sci.* **2013**, *17*, 307–308. [\[CrossRef\]](#)
245. Flor, H.; Nikolajsen, L.; Jensen, T.S. Phantom limb pain: A case of maladaptive CNS plasticity? *Nat. Rev. Neurosci.* **2006**, *7*, 873–881. [\[CrossRef\]](#)
246. Baron, R.; Hans, G.; Dickenson, A.H. Peripheral input and its importance for central sensitization. *Ann. Neurol.* **2013**, *74*, 630–636. [\[CrossRef\]](#)
247. Proske, U.; Gandevia, S.C. The proprioceptive senses: Their roles in signaling body shape, body position and movement, and muscle force. *Physiol. Rev.* **2012**, *92*, 1651–1697. [\[CrossRef\]](#) [\[PubMed\]](#)
248. Gay, A.; Aimonetti, J.M.; Roll, J.P.; Ribot-Ciscar, E. Kinesthetic illusions attenuate experimental muscle pain, as do muscle and cutaneous stimulation. *Brain Res.* **2015**, *1615*, 148–156. [\[CrossRef\]](#) [\[PubMed\]](#)
249. Wall, P.D. Pain, itch, and vibration. *Arch. Neurol.* **1960**, *2*, 365–375. [\[CrossRef\]](#) [\[PubMed\]](#)
250. Melzack, R.; Wall, P.D.; Weisz, A.Z. Masking and Metacontrast Phenomena in Skin Sensory System. *Exp. Neurol.* **1963**, *8*, 35–46. [\[CrossRef\]](#)
251. Melzack, R.; Schechter, B. Itch and vibration. *Science* **1965**, *147*, 1047–1048. [\[CrossRef\]](#)
252. Bank, P.J.M.; Peper, C.E.; Marinus, J.; Beek, P.J.; Van Hilten, J.J. Motor dysfunction of complex regional pain syndrome is related to impaired central processing of proprioceptive information. *J. Pain* **2013**, *14*, 1460–1474. [\[CrossRef\]](#)
253. Russell, W.R.; Spalding, J.M.K. Treatment of Painful Amputation Stumps. *Br. Med. J.* **1950**, *2*, 68. [\[CrossRef\]](#)
254. Livingston, W.K. *Pain Mechanisms*; Macmillan: New York, NY, USA, 1943.
255. Gordon, I.; Voos, A.C.; Bennett, R.H.; Bolling, D.Z.; Pelphrey, K.A.; Kaiser, M.D. Brain mechanisms for processing affective touch. *Hum. Brain Mapp.* **2013**, *34*, 914–922. [\[CrossRef\]](#)
256. Uvnäs-Moberg, K.; Handlin, L.; Petersson, M. Self-soothing behaviors with particular reference to oxytocin release induced by non-noxious sensory stimulation. *Front. Psychol.* **2014**, *5*, 1–16. [\[CrossRef\]](#)
257. Wu, J.Z.; Welcome, D.E.; Krajnak, K.; Dong, R.G. Finite element analysis of the penetrations of shear and normal vibrations into the soft tissues in a fingertip. *Med. Eng. Phys.* **2007**, *29*, 718–727. [\[CrossRef\]](#)
258. Welcome, D.E.; Krajnak, K.; Kashon, M.L.; Dong, R.G. An investigation on the biodynamic foundation of a rat tail vibration model. *Proc. Inst. Mech. Eng. Part H J. Eng. Med.* **2008**, *222*, 1127–1141. [\[CrossRef\]](#)
259. Curry, B.D.; Bain, J.L.W.; Yan, J.G.; Zhang, L.L.; Yamaguchi, M.; Matloub, H.S.; Riley, D.A. Vibration injury damages arterial endothelial cells. *Muscle Nerve* **2002**, *25*, 527–534. [\[CrossRef\]](#)
260. Lindblad, L.E.; Ekenvall, L. Alpha2-Adrenoceptor Inhibition in Patients with Vibration White Fingers. *Kurume Med. J.* **1990**, *37*, S95–S99. [\[CrossRef\]](#)
261. Eklund, G.; Hagbarth, K.E. Normal variability of tonic vibration reflexes in man. *Exp. Neurol.* **1966**, *16*, 80–92. [\[CrossRef\]](#) [\[PubMed\]](#)
262. Nakajima, T.; Izumizaki, M.; Sekihara, C.; Atsumi, T.; Homma, I. Combined effects of preceding muscle vibration and contraction on the tonic vibration reflex. *Exp. Brain Res.* **2009**, *192*, 211–219. [\[CrossRef\]](#) [\[PubMed\]](#)
263. Wood, S.A.; Gregory, J.E.; Proske, U. The influence of muscle spindle discharge on the human H reflex and the monosynaptic reflex in the cat. *J. Physiol.* **1996**, *497*, 279–290. [\[CrossRef\]](#) [\[PubMed\]](#)
264. Hultborn, H.; Illert, M.; Nielsen, J.; Paul, A.; Ballegaard, M.; Wiese, H. On the mechanism of the post-activation depression of the H-reflex in human subjects. *Exp. Brain Res.* **1996**, *108*, 450–462. [\[CrossRef\]](#)
265. Hagbarth, K.E.; Eklund, G. Motor effects of muscle vibration in spasticity, rigidity and cerebellar disorders. *Electroencephalogr. Clin. Neurophysiol.* **1968**, *25*, 407. [\[PubMed\]](#)

266. Paoloni, M.; Mangone, M.; Scettri, P.; Procaccianti, R.; Cometa, A.; Santilli, V. Segmental muscle vibration improves walking in chronic stroke patients with foot drop: A randomized controlled trial. *Neurorehabilit. Neural Repair* **2010**, *24*, 254–262. [\[CrossRef\]](#)
267. Paoloni, M.; Tavernese, E.; Fini, M.; Sale, P.; Franceschini, M.; Santilli, V.; Mangone, M. Segmental muscle vibration modifies muscle activation during reaching in chronic stroke: A pilot study. *NeuroRehabilitation* **2014**, *35*, 405–414. [\[CrossRef\]](#)
268. Alashram, A.R.; Padua, E.; Romagnoli, C.; Annino, G. Effectiveness of focal muscle vibration on hemiplegic upper extremity spasticity in individuals with stroke: A systematic review. *NeuroRehabilitation* **2019**, *45*, 471–481. [\[CrossRef\]](#)
269. Alashram, A.R.; Padua, E.; Romagnoli, C.; Raju, M.; Annino, G. Clinical effectiveness of focal muscle vibration on gait and postural stability in individuals with neurological disorders: A systematic review. *Physiother. Res. Int.* **2022**, *27*, e1945. [\[CrossRef\]](#)
270. Alghadir, A.H.; Anwer, S.; Zafar, H.; Iqbal, Z.A. Effect of localised vibration on muscle strength in healthy adults: a systematic review. *Physiotherapy* **2018**, *104*, 18–24. [\[CrossRef\]](#)
271. Fattorini, L.; Rodio, A.; Pettorossi, V.E.; Filippi, G.M. Is the focal muscle vibration an effective motor conditioning intervention? A systematic review. *J. Funct. Morphol. Kinesiol.* **2021**, *6*, 39. [\[CrossRef\]](#) [\[PubMed\]](#)
272. Germann, D.; El Bouse, A.; Shnier, J.; Abdelkader, N.; Kazemi, M. Effects of local vibration therapy on various performance parameters: A narrative literature review. *J. Can. Chiropr. Assoc.* **2018**, *62*, 170–181.
273. Murillo, N.; Valls-Sole, J.; Vidal, J.; Opisso, E.; Medina, J.; Kumru, H. Focal vibration in neurorehabilitation. *Eur. J. Phys. Rehabil. Med.* **2014**, *50*, 231–242. [\[PubMed\]](#)
274. Paolucci, T.; Pezzi, L.; La Verde, R.; Latessa, P.M.; Bellomo, R.G.; Saggini, R. The Focal Mechanical Vibration for Balance Improvement in Elderly —A Systematic Review. *Clin. Interv. Aging* **2021**, *16*, 2009–2021. [\[CrossRef\]](#) [\[PubMed\]](#)
275. Wang, H.; Chandrashekhara, R.; Rippetoe, J.; Ghazi, M. Focal Muscle Vibration for Stroke Rehabilitation: A Review of Vibration Parameters and Protocols. *Appl. Sci.* **2020**, *10*, 8270. [\[CrossRef\]](#)
276. Sadeghi, M.; Sawatzky, B. Effects of vibration on spasticity in individuals with spinal cord injury: A scoping systematic review. *Am. J. Phys. Med. Rehabil.* **2014**, *93*, 995–1007. [\[CrossRef\]](#)
277. Herda, T.J.; Ryan, E.D.; Smith, A.E.; Walter, A.A.; Bembien, M.G.; Stout, J.R.; Cramer, J.T. Acute effects of passive stretching vs vibration on the neuromuscular function of the plantar flexors. *Scand. J. Med. Sci. Sport.* **2009**, *19*, 703–713. [\[CrossRef\]](#)
278. Dickerson, C.; Gabler, G.; Hopper, K.; Kirk, D.; McGregor, C.J. Immediate effects of localized vibration on hamstring and quadriceps muscle performance. *Int. J. Sport. Phys. Ther.* **2012**, *7*, 381–387.
279. Pamukoff, D.N.; Ryan, E.D.; Troy Blackburn, J. The acute effects of local muscle vibration frequency on peak torque, rate of torque development, and EMG activity. *J. Electromyogr. Kinesiol.* **2014**, *24*, 888–894. [\[CrossRef\]](#)
280. Silva, H.R.; Couto, B.P.; Szmuchrowski, L.A. Effects of mechanical vibration applied in the opposite direction of muscle shortening on maximal isometric strength. *J. Strength Cond. Res.* **2008**, *22*, 1031–1036. [\[CrossRef\]](#)
281. Iodice, P.; Bellomo, R.G.; Gialluca, G.; Fanò, G.; Saggini, R. Acute and cumulative effects of focused high-frequency vibrations on the endocrine system and muscle strength. *Eur. J. Appl. Physiol.* **2011**, *111*, 897–904. [\[CrossRef\]](#)
282. Bosco, C.; Cardinale, M.; Tarpela, O. Influence of vibration on mechanical power and electromyogram activity in human arm flexor muscles. *Eur. J. Appl. Physiol. Occup. Physiol.* **1999**, *79*, 306–311. [\[CrossRef\]](#)
283. Cochrane, D.J. The Acute Effect of Direct Vibration on Muscular Power Performance in Master Athletes. *Int. J. Sport. Med.* **2016**, *37*, 144–148. [\[CrossRef\]](#)
284. Couto, B.P.; Silva, H.R.; Filho, A.G.; Da Silveira Neves, S.R.; Ramos, M.G.; Szmuchrowski, L.A.; Barbosa, M.P. Acute effects of resistance training with local vibration. *Int. J. Sport. Med.* **2013**, *34*, 814–819. [\[CrossRef\]](#)
285. Custer, L.; Peer, K.S.; Miller, L. The Effects of Local Vibration on Balance, Power, and Self-Reported Pain After Exercise. *J. Sport Rehabil.* **2017**, *26*, 193–201. [\[CrossRef\]](#)
286. Luo, J.; McNamara, B.; Moran, K. Effect of vibration training on neuromuscular output with ballistic knee extensions. *J. Sport. Sci.* **2008**, *26*, 1365–1373. [\[CrossRef\]](#)
287. Luo, J.; Clarke, M.; McNamara, B.; Moran, K. Influence of Resistance Load on Neuromuscular Response to Vibration Training. *J. Strength Cond. Res.* **2009**, *23*, 420–426. [\[CrossRef\]](#)
288. Moran, K.; McNamara, B.; Luo, J. Effect of vibration training in maximal effort (70% 1RM) dynamic bicep curls. *Med. Sci. Sport. Exerc.* **2007**, *39*, 526–533. [\[CrossRef\]](#)
289. Souron, R.; Farabet, A.; Féasson, L.; Belli, A.; Millet, G.Y.; Lapole, T. Eight weeks of local vibration training increases dorsiflexor muscle cortical voluntary activation. *J. Appl. Physiol.* **2017**, *122*, 1504–1515. [\[CrossRef\]](#)
290. Cannon, S.E.; Rues, J.P.; Melnick, M.E.; Guess, D. Head-erect behavior among three preschool-aged children with cerebral palsy. *Phys. Ther.* **1987**, *67*, 1198–1204. [\[CrossRef\]](#)
291. Tardieu, G.; Tardieu, C.; Lespargot, A.; Roby, A.; Bret, M.D. Can Vibration-Induced Illusions Be Used As a Muscle Perception Test for Normal and Cerebral-Palsied Children? *Dev. Med. Child Neurol.* **1984**, *26*, 449–456. [\[CrossRef\]](#) [\[PubMed\]](#)

292. Noma, T.; Matsumoto, S.; Etoh, S.; Shimodozono, M.; Kawahira, K. Anti-spastic effects of the direct application of vibratory stimuli to the spastic muscles of hemiplegic limbs in post-stroke patients. *Brain Inj.* **2009**, *23*, 623–631. [[CrossRef](#)] [[PubMed](#)]
293. Marconi, B.; Filippi, G.M.; Koch, G.; Giacobbe, V.; Pecchioli, C.; Versace, V.; Camerota, F.; Saraceni, V.M.; Caltagirone, C. Long-term effects on cortical excitability and motor recovery induced by repeated muscle vibration in chronic stroke patients. *Neurorehabilit. Neural Repair* **2011**, *25*, 48–60. [[CrossRef](#)] [[PubMed](#)]
294. Noma, T.; Matsumoto, S.; Shimodozono, M.; Etoh, S.; Kawahira, K. Anti-spastic effects of the direct application of vibratory stimuli to the spastic muscles of hemiplegic limbs in post-stroke patients: A proof-of-principle study. *J. Rehabil. Med.* **2012**, *44*, 325–330. [[CrossRef](#)] [[PubMed](#)]
295. Caliandro, P.; Celletti, C.; Padua, L.; Minciotti, I.; Russo, G.; Granata, G.; La Torre, G.; Granieri, E.; Camerota, F. Focal muscle vibration in the treatment of upper limb spasticity: A pilot randomized controlled trial in patients with chronic stroke. *Arch. Phys. Med. Rehabil.* **2012**, *93*, 1656–1661. [[CrossRef](#)]
296. Lee, S.W.; Cho, K.H.; Lee, W.H. Effect of a local vibration stimulus training programme on postural sway and gait in chronic stroke patients: A randomized controlled trial. *Clin. Rehabil.* **2013**, *27*, 921–931. [[CrossRef](#)]
297. Tavernese, E.; Paoloni, M.; Mangone, M.; Mandic, V.; Sale, P.; Franceschini, M.; Santilli, V. Segmental muscle vibration improves reaching movement in patients with chronic stroke. A randomized controlled trial. *NeuroRehabilitation* **2013**, *32*, 591–599. [[CrossRef](#)]
298. Casale, R.; Damiani, C.; Maestri, R.; Fundarò, C.; Chimento, P.; Foti, C. Localized 100 Hz vibration improves function and reduces upper limb spasticity: A double-blind controlled study. *Eur. J. Phys. Rehabil. Med.* **2014**, *50*, 495–504.
299. Costantino, C.; Galuppo, L.; Romiti, D. Efficacy of mechano-acoustic vibration on strength, pain, and function in poststroke rehabilitation: A pilot study. *Top. Stroke Rehabil.* **2014**, *21*, 391–399. [[CrossRef](#)]
300. Costantino, C.; Galuppo, L.; Romiti, D. Short-term effect of local muscle vibration treatment versus sham therapy on upper limb in chronic post-stroke patients: A randomized controlled trial. *Eur. J. Phys. Rehabil. Med.* **2017**, *53*, 32–40. [[CrossRef](#)]
301. Bonan, I.; Butet, S.; Jamal, K.; Yelnik, A.; Tasseel Ponche, S.; Leplaideur, S. Difference between individuals with left and right hemiparesis in the effect of gluteus medius vibration on body weight shifting. *Neurophysiol. Clin.* **2017**, *47*, 419–426. [[CrossRef](#)]
302. Calabrò, R.S.; Naro, A.; Russo, M.; Milardi, D.; Leo, A.; Filoni, S.; Trinchera, A.; Bramanti, P. Is two better than one? Muscle vibration plus robotic rehabilitation to improve upper limb spasticity and function: A pilot randomized controlled trial. *PLoS ONE* **2017**, *12*, e0185936. [[CrossRef](#)]
303. Celletti, C.; Sinibaldi, E.; Pierelli, F.; Monari, G.; Camerota, F. Focal Muscle Vibration and Progressive Modular Rebalancing with neurokinetic facilitations in post-stroke recovery of upper limb. *Clin. Ter.* **2017**, *168*, 33–36. [[CrossRef](#)]
304. Jung, S.M. The effects of vibratory stimulation employed to forearm and arm flexor muscles on upper limb function in patients with chronic stroke. *J. Phys. Ther. Sci.* **2017**, *29*, 1620–1622. [[CrossRef](#)]
305. Choi, W.H. Effects of repeated vibratory stimulation of wrist and elbow flexors on hand dexterity, strength, and sensory function in patients with chronic stroke: A pilot study. *J. Phys. Ther. Sci.* **2017**, *29*, 605–608. [[CrossRef](#)]
306. Toscano, M.; Celletti, C.; Viganò, A.; Altarocca, A.; Giuliani, G.; Jannini, T.B.; Mastria, G.; Ruggiero, M.; Maestrini, I.; Vicenzini, E.; et al. Short-term effects of focal muscle vibration on motor recovery after acute stroke: A pilot randomized sham-controlled study. *Front. Neurol.* **2019**, *10*, 1–9. [[CrossRef](#)]
307. Annino, G.; Alashram, A.R.; Alghwiri, A.A.; Romagnoli, C.; Messina, G.; Tancredi, V.; Padua, E.; Mercuri, N.B. Effect of segmental muscle vibration on upper extremity functional ability poststroke: A randomized controlled trial. *Medicine* **2019**, *98*, 1–5. [[CrossRef](#)]
308. Ayvat, F.; Özçakar, L.; Ayvat, E.; Aksu Yıldırım, S.; Kılınç, M. Effects of low vs. high frequency local vibration on mild-moderate muscle spasticity: Ultrasonographical and functional evaluation in patients with multiple sclerosis. *Mult. Scler. Relat. Disord.* **2021**, *51*. [[CrossRef](#)]
309. Camerota, F.; Celletti, C.; Suppa, A.; Galli, M.; Cimolin, V.; Filippi, G.M.; La Torre, G.; Albertini, G.; Stocchi, F.; De Pandis, M.F. Focal Muscle Vibration Improves Gait in Parkinson's Disease: A Pilot Randomized, Controlled Trial. *Mov. Disord. Clin. Pract.* **2016**, *3*, 559–566. [[CrossRef](#)]
310. Özvar, G.B.; Ayvat, E.; Kılınç, M. Immediate Effects of Local Vibration and Whole-body Vibration on Postural Control in Patients with Ataxia: An Assessor-Blind, Cross-over randomized trial. *Cerebellum* **2021**, *20*, 83–91. [[CrossRef](#)]
311. Calancie, B.; Broton, J.G.; John Klose, K.; Traad, M.; Difini, J.; Ram Ayyar, D. Evidence that alterations in presynaptic inhibition contribute to segmental hypo- and hyperexcitability after spinal cord injury in man. *Electroencephalogr. Clin. Neurophysiol. Evoked Potentials* **1993**, *89*, 177–186. [[CrossRef](#)] [[PubMed](#)]
312. Taylor, S.; Ashby, P.; Verrier, M. Neurophysiological changes following traumatic spinal lesions in man. *J. Neurol. Neurosurg. Psychiatry* **1984**, *47*, 1102–1108. [[CrossRef](#)] [[PubMed](#)]

313. Hilgevoord, A.A.J.; Bour, L.J.; Koelman, J.H.T.M.; Ongerboer De Visser, B.W. The relationship between the soleus H-reflex amplitude and vibratory inhibition in controls and spastic subjects. II. Computer model. *J. Electromyogr. Kinesiol.* **1996**, *6*, 259–266. [[CrossRef](#)] [[PubMed](#)]
314. Celletti, C.; Fattorini, L.; Camerota, F.; Ricciardi, D.; La Torre, G.; Landi, F.; Filippi, G.M. Focal muscle vibration as a possible intervention to prevent falls in elderly women: A pragmatic randomized controlled trial. *Aging Clin. Exp. Res.* **2015**, *27*, 857–863. [[CrossRef](#)] [[PubMed](#)]
315. Ehsani, H.; Mohler, J.; Marlinski, V.; Rashedi, E.; Toosizadeh, N. The influence of mechanical vibration on local and central balance control. *J. Biomech.* **2018**, *71*, 59–66. [[CrossRef](#)]
316. Filippi, G.M.; Brunetti, O.; Botti, F.M.; Panichi, R.; Roscini, M.; Camerota, F.; Cesari, M.; Pettorossi, V.E. Improvement of Stance Control and Muscle Performance Induced by Focal Muscle Vibration in Young-Elderly Women: A Randomized Controlled Trial. *Arch. Phys. Med. Rehabil.* **2009**, *90*, 2019–2025. [[CrossRef](#)]
317. Rabini, A.; De Sire, A.; Marzetti, E.; Gimigliano, R.; Ferriero, G.; Piazzini, D.B.; Iolascon, G.; Gimigliano, F. Effects of focal muscle vibration on physical functioning in patients with knee osteoarthritis: A randomized controlled trial. *Eur. J. Phys. Rehabil. Med.* **2015**, *51*, 513–520.
318. Wanderley, F.S.; Alburquerque-Sendn, F.; Parizotto, N.A.; Rebelatto, J.R. Effect of plantar vibration stimuli on the balance of older women: A randomized controlled trial. *Arch. Phys. Med. Rehabil.* **2011**, *92*, 199–206. [[CrossRef](#)]
319. Yu, M.; Piao, Y.J.; Kim, S.H.; Kim, D.W.; Kim, N.G. Effects of tendon vibration during one- legged and two-legged stance in elderly individuals. *Int. J. Precis. Eng. Manuf.* **2010**, *11*, 969–977. [[CrossRef](#)]
320. Kamada, K.; Shimodozono, M.; Hamada, H.; Kawahira, K. Effects of 5 minutes of neck-muscle vibration immediately before occupational therapy on unilateral spatial neglect. *Disabil. Rehabil.* **2011**, *33*, 2322–2328. [[CrossRef](#)]
321. Paoloni, M.; Giovannelli, M.; Mangone, M.; Leonardi, L.; Tavernese, E.; Di Pangrazio, E.; Bernetti, A.; Santilli, V.; Pozzilli, C. Does giving segmental muscle vibration alter the response to botulinum toxin injections in the treatment of spasticity in people with multiple sclerosis? A single-blind randomized controlled trial. *Clin. Rehabil.* **2013**, *27*, 803–812. [[CrossRef](#)]
322. Novak, P.; Novak, V. Effect of step-synchronized vibration stimulation of soles on gait in Parkinson's disease: A pilot study. *J. NeuroEngineering Rehabil.* **2006**, *3*, 1–7. [[CrossRef](#)]
323. Rosenkranz, K.; Butler, K.; Williamon, A.; Rothwell, J.C. Regaining motor control in musician's dystonia by restoring sensorimotor organization. *J. Neurosci.* **2009**, *29*, 14627–14636. [[CrossRef](#)]
324. Fattorini, L.; Ferraresi, A.; Rodio, A.; Azzena, G.B.; Filippi, G.M. Motor performance changes induced by muscle vibration. *Eur. J. Appl. Physiol.* **2006**, *98*, 79–87. [[CrossRef](#)]
325. Casale, R.; Ring, H.; Rainoldi, A. High frequency vibration conditioning stimulation centrally reduces myoelectrical manifestation of fatigue in healthy subjects. *J. Electromyogr. Kinesiol.* **2009**, *19*, 998–1004. [[CrossRef](#)]
326. Lapole, T.; Pérot, C. Effects of repeated Achilles tendon vibration on triceps surae force production. *J. Electromyogr. Kinesiol.* **2010**, *20*, 648–654. [[CrossRef](#)]
327. Brunetti, O.; Botti, F.M.; Roscini, M.; Brunetti, A.; Panichi, R.; Filippi, G.M.; Biscarini, A.; Pettorossi, V.E. Focal vibration of quadriceps muscle enhances leg power and decreases knee joint laxity in female volleyball players. *J. Sport. Med. Phys. Fit.* **2012**, *52*, 596–605.
328. Brunetti, O.; Botti, F.M.; Brunetti, A.; Biscarini, A.; Scarponi, A.M.; Filippi, G.M.; Pettorossi, V.E. Effects of focal vibration on bone mineral density and motor performance of postmenopausal osteoporotic women. *J. Sport. Med. Phys. Fit.* **2015**, *55*, 118–127.
329. Filippi, G.M.; Fattorini, L.; Summa, A.; Zagaglia, A.; Rodio, A. Effects of focal vibration on power and work in multiple wingate tests. *Biol. Sport* **2020**, *37*, 25–31. [[CrossRef](#)]
330. Ritzmann, R.; Stark, C.; Krause, A. Vibration therapy in patients with cerebral palsy: A systematic review. *Neuropsychiatr. Dis. Treat.* **2018**, *14*, 1607–1625. [[CrossRef](#)]
331. Marazzi, S.; Kiper, P.; Palmer, K.; Agostini, M.; Turolla, A. Effects of vibratory stimulation on balance and gait in Parkinson's disease: A systematic review and meta-analysis. *Eur. J. Phys. Rehabil. Med.* **2021**, *57*, 254–264. [[CrossRef](#)] [[PubMed](#)]
332. Avvantaggiato, C.; Casale, R.; Cinone, N.; Facciorusso, S.; Turitto, A.; Stuppiello, L.; Picelli, A.; Ranieri, M.; Intiso, D.; Fiore, P.; et al. Localized muscle vibration in the treatment of motor impairment and spasticity in post-stroke patients: A systematic review. *Eur. J. Phys. Rehabil. Med.* **2021**, *57*, 44–60. [[CrossRef](#)] [[PubMed](#)]
333. Mortaza, N.; Abou-Setta, A.M.; Zarychanski, R.; Loewen, H.; Rabbani, R.; Glazebrook, C.M. Upper limb tendon/muscle vibration in persons with subacute and chronic stroke: A systematic review and meta-analysis. *Eur. J. Phys. Rehabil. Med.* **2019**, *55*, 558–569. [[CrossRef](#)] [[PubMed](#)]
334. Etoom, M.; Khraiweh, Y.; Lena, F.; Hawamdeh, M.; Hawamdeh, Z.; Centonze, D.; Foti, C. Effectiveness of Physiotherapy Interventions on Spasticity in People with Multiple Sclerosis: A Systematic Review and Meta-Analysis. *Am. J. Phys. Med. Rehabil.* **2018**, *97*, 793–807. [[CrossRef](#)] [[PubMed](#)]
335. Celletti, C.; Suppa, A.; Bianchini, E.; Lakin, S.; Toscano, M.; La Torre, G.; Di Piero, V.; Camerota, F. Promoting post-stroke recovery through focal or whole body vibration: Criticisms and prospects from a narrative review. *Neurol. Sci.* **2020**, *41*, 11–24. [[CrossRef](#)]

336. Grünewald, R.A.; Yoneda, Y.; Shipman, J.M.; Sagar, H.J. Idiopathic focal dystonia: A disorder of muscle spindle afferent processing? *Brain* **1997**, *120*, 2179–2185. [[CrossRef](#)]
337. Yoneda, Y.; Rome, S.; Sagar, H.J.; Grünewald, R.A. Abnormal perception of the tonic vibration reflex in idiopathic focal dystonia. *Eur. J. Neurol.* **2000**, *7*, 529–533. [[CrossRef](#)]
338. Trompetto, C.; Currà, A.; Buccolieri, A.; Suppa, A.; Abbruzzese, G.; Berardelli, A. Botulinum toxin changes intrafusal feedback in dystonia: A study with the tonic vibration reflex. *Mov. Disord.* **2006**, *21*, 777–782. [[CrossRef](#)]
339. Conte, A.; Defazio, G.; Hallett, M.; Fabbrini, G.; Berardelli, A. The role of sensory information in the pathophysiology of focal dystonias. *Nat. Rev. Neurol.* **2019**, *15*, 224–233. [[CrossRef](#)]
340. Kaji, R.; Rothwell, J.C.; Katayama, M.; Ikeda, T.; Kubori, T.; Kohara, N.; Mezaki, T.; Shibasaki, H.; Kimura, J. Tonic vibration reflex and muscle afferent block in writer's cramp. *Ann. Neurol.* **1995**, *38*, 155–162. [[CrossRef](#)]
341. Boychuk, J.A.; Schwerin, S.C.; Thomas, N.; Roger, A.; Silvera, G.; Liverpool, M.; Adkins, D.L.; Kleim, J.A. Enhanced Motor Recovery after Stroke with Combined Cortical Stimulation and Rehabilitative Training Is Dependent on Infarct Location. *Neurorehabilit. Neural Repair* **2016**, *30*, 173–181. [[CrossRef](#)]
342. Ekblom, M.M.N.; Thorstensson, A. Effects of prolonged vibration on H-Reflexes, muscle activation, and dynamic strength. *Med. Sci. Sport. Exerc.* **2011**, *43*, 1933–1939. [[CrossRef](#)]
343. Xu, L.; Cardinale, M.; Rabotti, C.; Beju, B.; Mischi, M. Eight-Week Vibration Training of the Elbow Flexors by Force Modulation. *J. Strength Cond. Res.* **2016**, *30*, 739–746. [[CrossRef](#)]
344. Lundborg, G.; Dahlin, L.B.; Hansson, H.A.; Kanje, M.; Necking, L.E. Vibration exposure and peripheral nerve fiber damage. *J. Hand Surg.* **1990**, *15*, 346–351. [[CrossRef](#)]
345. Chang, K.Y.; Ho, S.T.; Yu, H.S. Vibration induced neurophysiological and electron microscopical changes in rat peripheral nerves. *Occup. Environ. Med.* **1994**, *51*, 130–135. [[CrossRef](#)]
346. Uryash, A.; Wu, H.; Bassuk, J.; Kurlansky, P.; Sackner, M.A.; Adams, J.A. Low-amplitude pulses to the circulation through periodic acceleration induces endothelial-dependent vasodilatation. *J. Appl. Physiol.* **2009**, *106*, 1840–1847. [[CrossRef](#)]
347. Martínez, A.; Arias, J.; Bassuk, J.A.; Wu, H.; Kurlansky, P.; Adams, J.A. Adrenomedullin is increased by pulsatile shear stress on the vascular endothelium via periodic acceleration (pGz). *Peptides* **2008**, *29*, 73–78. [[CrossRef](#)]
348. White, C.R.; Haidekker, M.A.; Stevens, H.Y.; Frangos, J.A. Extracellular signal-regulated kinase activation and endothelin-1 production in human endothelial cells exposed to vibration. *J. Physiol.* **2004**, *555*, 565–572. [[CrossRef](#)]
349. Johnson, P.K.; Feland, J.B.; Johnson, A.W.; Mack, G.W.; Mitchell, U.H. Effect of whole body vibration on skin blood flow and nitric oxide production. *J. Diabetes Sci. Technol.* **2014**, *8*, 889–894. [[CrossRef](#)]
350. Chien, S. Mechanotransduction and endothelial cell homeostasis: The wisdom of the cell. *Am. J. Physiol.-Heart Circ. Physiol.* **2007**, *292*. [[CrossRef](#)]
351. Ueda, A.; Koga, M.; Ikeda, M.; Kudo, S.; Tanishita, K. Effect of shear stress on microvessel network formation of endothelial cells with in vitro three-dimensional model. *Am. J. Physiol.-Heart Circ. Physiol.* **2004**, *287*. [[CrossRef](#)] [[PubMed](#)]
352. Zeng, W.; Christensen, L.P.; Tomanek, R.J. Differential effects of cyclic and static stretch on coronary microvascular endothelial cell receptors and vasculogenic/angiogenic responses. *Am. J. Physiol.-Heart Circ. Physiol.* **2008**, *295*. [[CrossRef](#)]
353. Ruehle, M.A.; Eastburn, E.A.; Labelle, S.A.; Krishnan, L.; Weiss, J.A.; Boerckel, J.D.; Wood, L.B.; Guldborg, R.E.; Willett, N.J. Extracellular matrix compression temporally regulates microvascular angiogenesis. *Sci. Adv.* **2020**, *6*, eabb6351. [[CrossRef](#)] [[PubMed](#)]
354. Moore, K.A.; Polte, T.; Huang, S.; Shi, B.; Alsberg, E.; Sunday, M.E.; Ingber, D.E. Control of basement membrane remodeling and epithelial branching morphogenesis in embryonic lung by Rho and cytoskeletal tension. *Dev. Dyn.* **2005**, *232*, 268–281. [[CrossRef](#)] [[PubMed](#)]
355. Mammoto, A.; Connor, K.M.; Mammoto, T.; Yung, C.W.; Huh, D.; Aderman, C.M.; Mostoslavsky, G.; Smith, L.E.; Ingber, D.E. A mechanosensitive transcriptional mechanism that controls angiogenesis. *Nature* **2009**, *457*, 1103–1108. [[CrossRef](#)]
356. Wu, Y.; Al-Ameen, M.A.; Ghosh, G. Integrated Effects of Matrix Mechanics and Vascular Endothelial Growth Factor (VEGF) on Capillary Sprouting. *Ann. Biomed. Eng.* **2014**, *42*, 1024–1036. [[CrossRef](#)]
357. Huang, S.; Ingber, D.E. The structural and mechanical complexity of cell-growth control. *Nat. Cell Biol.* **1999**, *1*, E131–E138. [[CrossRef](#)]
358. Folkman, J.; Moscona, A. Role of cell shape in growth control. *Nature* **1978**, *273*, 345–349. [[CrossRef](#)]
359. Nauli, S.M.; Kawanabe, Y.; Kaminski, J.J.; Pearce, W.J.; Ingber, D.E.; Zhou, J. Endothelial Cilia Are Fluid Shear Sensors That Regulate Calcium Signaling and Nitric Oxide Production Through Polycystin-1. *Circulation* **2008**, *117*, 1161–1171. [[CrossRef](#)]
360. Bromann, P.A.; Korkaya, H.; Courtneidge, S.A. The interplay between Src family kinases and receptor tyrosine kinases. *Oncogene* **2004**, *23*, 7957–7968. [[CrossRef](#)]
361. Conway, D.; Schwartz, M.A. Lessons from the endothelial junctional mechanosensory complex. *F1000 Biol. Rep.* **2012**, *4*, 2–7. [[CrossRef](#)]

362. Hood, J.D.; Meininger, C.J.; Ziche, M.; Granger, H.J. VEGF upregulates eNOS message, protein, and NO production in human endothelial cells. *Am. J. Physiol.-Heart Circ. Physiol.* **1998**, *274*, H1054–H1058. [[CrossRef](#)]
363. Van Der Zee, R.; Murohara, T.; Luo, Z.; Zollmann, F.; Passeri, J.; Lekutat, C.; Isner, J.M. Vascular endothelial growth factor/vascular permeability factor augments nitric oxide release from quiescent rabbit and human vascular endothelium. *Circulation* **1997**, *95*, 1030–1037. [[CrossRef](#)]
364. Cooke, J.P.; Losordo, D.W. Nitric Oxide and Angiogenesis. *Circulation* **2002**, *105*, 2133–2135. . 14928.45119.73. [[CrossRef](#)]
365. Tzima, E.; Irani-Tehrani, M.; Kiosses, W.B.; Dejana, E.; Schultz, D.A.; Engelhardt, B.; Cao, G.; DeLisser, H.; Schwartz, M.A. A mechanosensory complex that mediates the endothelial cell response to fluid shear stress. *Nature* **2005**, *437*, 426–431. [[CrossRef](#)]
366. Losordo, D.W.; Isner, J.M. Vascular endothelial growth factor-induced angiogenesis: Crouching tiger or hidden dragon? *J. Am. Coll. Cardiol.* **2001**, *37*, 2131–2135. [[CrossRef](#)]
367. Friedrich, E.E.; Hong, Z.; Xiong, S.; Zhong, M.; Di, A.; Rehman, J.; Komarova, Y.A.; Malik, A.B. Endothelial cell Piezo1 mediates pressure-induced lung vascular hyperpermeability via disruption of adherens junctions. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 12980–12985. [[CrossRef](#)]
368. Wang, S.; Aurora, A.B.; Johnson, B.A.; Qi, X.; McAnally, J.; Hill, J.A.; Richardson, J.A.; Bassel-Duby, R.; Olson, E.N. The Endothelial-Specific MicroRNA miR-126 Governs Vascular Integrity and Angiogenesis. *Dev. Cell* **2008**, *15*, 261–271. [[CrossRef](#)]
369. Chamorro-Jorganes, A.; Lee, M.Y.; Araldi, E.; Landskroner-Eiger, S.; Fernández-Fuertes, M.; Sahraei, M.; Quiles Del Rey, M.; Van Solingen, C.; Yu, J.; Fernández-Hernando, C.; et al. VEGF-Induced Expression of miR-17-92 Cluster in Endothelial Cells Is Mediated by ERK/ELK1 Activation and Regulates Angiogenesis. *Circ. Res.* **2016**, *118*, 38–47. [[CrossRef](#)]
370. Hong, S.G.; Shin, J.; Aldokhayyil, M.; Brown, M.D.; Park, J.Y. Mitochondrial and Metabolic Adaptations to Exercise-Induced Fluid Shear Stress in Endothelial Cells. *Exerc. Sport Sci. Rev.* **2022**, *50*, 145–155. [[CrossRef](#)]
371. Chiu, J.J.; Chien, S. Effects of disturbed flow on vascular endothelium: Pathophysiological basis and clinical perspectives. *Physiol. Rev.* **2011**, *91*, 327–387. [[CrossRef](#)] [[PubMed](#)]
372. Mammoto, T.; Ingber, D.E. Mechanical control of tissue and organ development. *Development* **2010**, *137*, 1407–1420. [[CrossRef](#)] [[PubMed](#)]
373. Lucitti, J.L.; Jones, E.A.V.; Huang, C.; Chen, J.; Fraser, S.E.; Dickinson, M.E. Vascular remodeling of the mouse yolk sac requires hemodynamic force. *Development* **2007**, *134*, 3317–3326. [[CrossRef](#)] [[PubMed](#)]
374. Song, J.W.; Munn, L.L. Fluid forces control endothelial sprouting. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 15342–15347. [[CrossRef](#)] [[PubMed](#)]
375. Dolan, J.M.; Kolega, J.; Meng, H. High wall shear stress and spatial gradients in vascular pathology: A review. *Ann. Biomed. Eng.* **2013**, *41*, 1411–1427. [[CrossRef](#)]
376. Vanhoutte, P.M.; Shimokawa, H.; Tang, E.H.C.; Feletou, M. Endothelial dysfunction and vascular disease. *Acta Physiol.* **2009**, *196*, 193–222. [[CrossRef](#)]
377. Zhou, J.; Li, Y.S.; Chien, S. Shear stress-initiated signaling and its regulation of endothelial function. *Arterioscler. Thromb. Vasc. Biol.* **2014**, *34*, 2191–2198. [[CrossRef](#)]
378. Iring, A.; Jin, Y.J.; Albarrán-Juárez, J.; Siragusa, M.; Wang, S.P.; Dancs, P.T.; Nakayama, A.; Tonack, S.; Chen, M.; Künne, C.; et al. Shear stress-induced endothelial adrenomedullin signaling regulates vascular tone and blood pressure. *J. Clin. Investig.* **2019**, *129*, 2775–2791. [[CrossRef](#)]
379. Hahn, C.; Schwartz, M.A. Mechanotransduction in vascular physiology and atherogenesis. *Nat. Rev. Mol. Cell Biol.* **2009**, *10*, 53–62. [[CrossRef](#)]
380. Gimbrone, M.A.; García-Cardena, G. Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. *Circ. Res.* **2016**, *118*, 620–636. [[CrossRef](#)]
381. Davies, P.F.; Spaan, J.A.; Krams, R. Shear stress biology of the endothelium. *Ann. Biomed. Eng.* **2005**, *33*, 1714–1718. [[CrossRef](#)]
382. Balligand, J.L.; Feron, O.; Dessy, C. eNOS Activation by Physical Forces: From Short-Term Regulation of Contraction to Chronic Remodeling of Cardiovascular Tissues. *Physiol. Rev.* **2009**, *89*, 481–534. [[CrossRef](#)]
383. Ziche, M.; Morbidelli, L.; Masini, E.; Amerini, S.; Granger, H.J.; Maggi, C.A.; Geppetti, P.; Ledda, F. Nitric oxide mediates angiogenesis in vivo and endothelial cell growth and migration in vitro promoted by substance P. *J. Clin. Investig.* **1994**, *94*, 2036–2044. [[CrossRef](#)]
384. Morley, L.C.; Shi, J.; Gaunt, H.J.; Hyman, A.J.; Webster, P.J.; Williams, C.; Forbes, K.; Walker, J.J.; Simpson, N.A.B.; Beech, D.J. Piezo1 channels are mechanosensors in human fetoplacental endothelial cells. *Mol. Hum. Reprod.* **2018**, *24*, 510–520. [[CrossRef](#)]
385. Fish, J.E.; Santoro, M.M.; Morton, S.U.; Yu, S.; Yeh, R.F.; Wythe, J.D.; Ivey, K.N.; Bruneau, B.G.; Stainier, D.Y.R.; Srivastava, D. miR-126 Regulates Angiogenic Signaling and Vascular Integrity. *Dev. Cell* **2008**, *15*, 272–284. . [[CrossRef](#)]
386. Harris, T.A.; Yamakuchi, M.; Ferlito, M.; Mendell, J.T.; Lowenstein, C.J. MicroRNA-126 regulates endothelial expression of vascular cell adhesion molecule 1. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 1516–1521. [[CrossRef](#)]
387. Zhang, J.; Zhang, Z.; Zhang, D.Y.; Zhu, J.; Zhang, T.; Wang, C. MicroRNA 126 inhibits the transition of endothelial progenitor cells to mesenchymal cells via the PIK3R2-PI3K/Akt signalling pathway. *PLoS ONE* **2013**, *8*, e83294. [[CrossRef](#)]

388. Png, K.J.; Halberg, N.; Yoshida, M.; Tavazoie, S.F. A microRNA regulon that mediates endothelial recruitment and metastasis by cancer cells. *Nature* **2012**, *481*, 190–196. [[CrossRef](#)]
389. Yang, Y.; Wang, D.; Zhang, C.; Yang, W.; Li, C.; Gao, Z.; Pei, K.; Li, Y. Piezo1 mediates endothelial atherogenic inflammatory responses via regulation of YAP/TAZ activation. *Hum. Cell* **2022**, *35*, 51–62. [[CrossRef](#)]
390. Chen, X.; Liang, H.; Zhang, J.; Zen, K.; Zhang, C.Y. Secreted microRNAs: A new form of intercellular communication. *Trends Cell Biol.* **2012**, *22*, 125–132. [[CrossRef](#)]
391. Domańska-Senderowska, D.; Laguette, M.J.N.; Jegier, A.; Cieszczyk, P.; September, A.V.; Brzezińska-Lasota, E. MicroRNA Profile and Adaptive Response to Exercise Training: A Review. *Int. J. Sport. Med.* **2019**, *40*, 227–235. [[CrossRef](#)]
392. Sabirin, R.M.; Yunus, J.; Agustini, D. The effects of aerobic exercise on blood plasma microRNA level in healthy adults: A systematic review and meta-analysis. *Sport Sci. for Health* **2022**, 1–16. [[CrossRef](#)]
393. Celic, T.; Meuth, V.; Six, I.; Massy, Z.; Metzinger, L. The mir-221/222 Cluster is a Key Player in Vascular Biology via the Fine-Tuning of Endothelial Cell Physiology. *Curr. Vasc. Pharmacol.* **2016**, *15*, 40–46. [[CrossRef](#)] [[PubMed](#)]
394. Urbich, C.; Kuehnbacher, A.; Dimmeler, S. Role of microRNAs in vascular diseases, inflammation, and angiogenesis. *Cardiovasc. Res.* **2008**, *79*, 581–588. [[CrossRef](#)] [[PubMed](#)]
395. Grinsell, D.; Keating, C.P. Peripheral Nerve Reconstruction after Injury: A Review of Clinical and Experimental Therapies. *BioMed Res. Int.* **2014**, *2014*. [[CrossRef](#)]
396. Song, B.W.; Oh, S.; Chang, W. Multiplexed targeting of microRNA in stem cell-derived extracellular vesicles for regenerative medicine. *BMB Rep.* **2022**, *55*, 65–71. [[CrossRef](#)]
397. Esposito, E.; Hayakawa, K.; Maki, T.; Arai, K.; Lo, E.H. Effects of Postconditioning on Neurogenesis and Angiogenesis during the Recovery Phase after Focal Cerebral Ischemia. *Stroke* **2015**, *46*, 2691–2694. [[CrossRef](#)]
398. Katsimpardi, L.; Litterman, N.K.; Schein, P.A.; Miller, C.M.; Loffredo, F.S.; Wojtkiewicz, G.R.; Chen, J.W.; Lee, R.T.; Wagers, A.J.; Rubin, L.L. Vascular and Neurogenic Rejuvenation of the Aging Mouse Brain by Young Systemic Factors. *Science* **2014**, *344*, 630–634. [[CrossRef](#)]
399. Ma, J.; Zhang, L.; He, G.; Tan, X.; Jin, X.; Li, C. Transcutaneous auricular vagus nerve stimulation regulates expression of growth differentiation factor 11 and activin-like kinase 5 in cerebral ischemia/reperfusion rats. *J. Neurol. Sci.* **2016**, *369*, 27–35. [[CrossRef](#)]
400. Carmeliet, P. Blood vessels and nerves: Common signals, pathways and diseases. *Nat. Rev. Genet.* **2003**, *4*, 710–720. [[CrossRef](#)]
401. Plummer, P.N.; Freeman, R.; Taft, R.J.; Vider, J.; Sax, M.; Umer, B.A.; Gao, D.; Johns, C.; Mattick, J.S.; Wilton, S.D.; et al. MicroRNAs regulate tumor angiogenesis modulated by endothelial progenitor cells. *Cancer Res.* **2013**, *73*, 341–352. [[CrossRef](#)]
402. Kuehnbacher, A.; Urbich, C.; Zeiher, A.M.; Dimmeler, S. Role of Dicer and Drosha for endothelial microRNA expression and angiogenesis. *Circ. Res.* **2007**, *101*, 59–68. [[CrossRef](#)]
403. Heusschen, R.; van Gink, M.; Griffioen, A.W.; Thijssen, V.L. MicroRNAs in the tumor endothelium: Novel controls on the angioregulatory switchboard. *Biochim. Et Biophys. Acta-Rev. Cancer* **2010**, *1805*, 87–96. [[CrossRef](#)]
404. Ma, S.; Zhang, A.; Li, X.; Zhang, S.; Liu, S.; Zhao, H.; Wu, S.; Chen, L.; Ma, C.; Zhao, H. MiR-21-5p regulates extracellular matrix degradation and angiogenesis in TMJOA by targeting Spry1. *Arthritis Res. Ther.* **2020**, *22*, 1–17. [[CrossRef](#)]
405. Suárez, Y.; Fernández-Hernando, C.; Yu, J.; Gerber, S.A.; Harrison, K.D.; Pober, J.S.; Iruela-Arispe, M.L.; Merkenschlager, M.; Sessa, W.C. Dicer-dependent endothelial microRNAs are necessary for postnatal angiogenesis. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 14082–14087. [[CrossRef](#)]
406. Semo, J.; Sharir, R.; Afek, A.; Avivi, C.; Barshack, I.; Maysel-Auslender, S.; Krelin, Y.; Kain, D.; Entin-Meer, M.; Keren, G.; et al. The 106b~25 microRNA cluster is essential for neovascularization after hindlimb ischaemia in mice. *Eur. Heart J.* **2014**, *35*, 3212–3223. [[CrossRef](#)]
407. Gallach, S.; Calabuig-Fariñas, S.; Jantus-Lewintre, E.; Camps, C. MicroRNAs: Promising new antiangiogenic targets in cancer. *BioMed Res. Int.* **2014**, *2014*. [[CrossRef](#)]
408. Anand, S.; Majeti, B.K.; Acevedo, L.M.; Murphy, E.A.; Mukthavaram, R.; Scheppke, L.; Huang, M.; Shields, D.J.; Lindquist, J.N.; Lapinski, P.E.; et al. MicroRNA-132-mediated loss of p120RasGAP activates the endothelium to facilitate pathological angiogenesis. *Nat. Med.* **2010**, *16*, 909–914. [[CrossRef](#)]
409. Umez, T.; Tadokoro, H.; Azuma, K.; Yoshizawa, S.; Ohyashiki, K.; Ohyashiki, J.H. Exosomal miR-135b shed from hypoxic multiple myeloma cells enhances angiogenesis by targeting factor-inhibiting HIF-1. *Blood* **2014**, *124*, 3748–3757. [[CrossRef](#)]
410. Fasanaro, P.; D'Alessandra, Y.; Di Stefano, V.; Melchionna, R.; Romani, S.; Pompilio, G.; Capogrossi, M.C.; Martelli, F. MicroRNA-210 modulates endothelial cell response to hypoxia and inhibits the receptor tyrosine kinase ligand ephrin-A3. *J. Biol. Chem.* **2008**, *283*, 15878–15883. [[CrossRef](#)]
411. Li, H.; Ouyang, X.P.; Jiang, T.; Zheng, X.L.; He, P.P.; Zhao, G.J. MicroRNA-296: A promising target in the pathogenesis of atherosclerosis? *Mol. Med.* **2018**, *24*, 1–8. [[CrossRef](#)] [[PubMed](#)]
412. Lee, D.Y.; Deng, Z.; Wang, C.H.; Yang, B.B. MicroRNA-378 promotes cell survival, tumor growth, and angiogenesis by targeting SuFu and Fus-1 expression. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 20350–20355. [[CrossRef](#)] [[PubMed](#)]
413. Floriano, J.F.; Emanueli, C.; Vega, S.; Barbosa, A.M.P.; Oliveira, R.G.D.; Floriano, E.A.F.; Graeff, C.F.D.O.; Abbade, J.F.; Herculano, R.D.; Sobrevia, L.; et al. Pro-angiogenic approach for skeletal muscle regeneration. *Biochim. Et Biophys. Acta-Gen. Subj.* **2022**, 1866. [[CrossRef](#)] [[PubMed](#)]
414. Goren, V.; Brehm, M.U.; Koch, A.; Hagen, A. Growth factors for angiogenesis in peripheral arterial disease. *Cochrane Database Syst. Rev.* **2015**, *2015*. [[CrossRef](#)]

415. Nascimento, A.I.; Mar, F.M.; Sousa, M.M. The intriguing nature of dorsal root ganglion neurons: Linking structure with polarity and function. *Prog. Neurobiol.* **2018**, *168*, 86–103. [\[CrossRef\]](#)
416. Rigoni, M.; Negro, S. Signals Orchestrating Peripheral Nerve Repair. *Cells* **2020**, *9*, 1768. [\[CrossRef\]](#)
417. Ziv, N.E.; Spira, M.E. Axotomy induces a transient and localized elevation of the free intracellular calcium concentration to the millimolar range. *J. Neurophysiol.* **1995**, *74*, 2625–2637. [\[CrossRef\]](#)
418. Ziv, N.E.; Spira, M.E. Localized and transient elevations of intracellular Ca²⁺ induce the dedifferentiation of axonal segments into growth cones. *J. Neurosci.* **1997**, *17*, 3568–3579. [\[CrossRef\]](#)
419. Cho, Y.; Sloutsky, R.; Naegle, K.M.; Cavalli, V. Injury-Induced HDAC5 nuclear export is essential for axon regeneration. *Cell* **2013**, *155*, 894. [\[CrossRef\]](#)
420. Rishal, I.; Fainzilber, M. Axon-soma communication in neuronal injury. *Nat. Rev. Neurosci.* **2014**, *15*, 32–42. [\[CrossRef\]](#)
421. Yoo, S.; van Niekerk, E.A.; Merianda, T.T.; Twiss, J.L. Dynamics of axonal mRNA transport and implications for peripheral nerve regeneration. *Exp. Neurol.* **2010**, *223*, 19–27. [\[CrossRef\]](#)
422. Czogalla, A.; Sikorski, A.F. Spectrin and calpain: A ‘target’ and a ‘sniper’ in the pathology of neuronal cells. *Cell. Mol. Life Sci.* **2005**, *62*, 1913–1924. [\[CrossRef\]](#)
423. Yoo, S.; Nguyen, M.P.; Fukuda, M.; Bittner, G.D.; Fishman, H.M. Plasmalemmal Sealing of Transected Mammalian Neurites Is a Gradual Process Mediated by Ca²⁺-Regulated Proteins. *J. Neurosci. Res.* **2003**, *74*, 541–551. [\[CrossRef\]](#) [\[PubMed\]](#)
424. Gitler, D.; Spira, M.E. Real time imaging of calcium-induced localized proteolytic activity after axotomy and its relation to growth cone formation. *Neuron* **1998**, *20*, 1123–1135. [\[CrossRef\]](#)
425. Gitler, D.; Spira, M.E. Short window of opportunity for calpain induced growth cone formation after axotomy of Aplysia neurons. *J. Neurobiol.* **2002**, *52*, 267–279. [\[CrossRef\]](#)
426. Jessen, K.R.; Mirsky, R.; Lloyd, A.C. Schwann cells: Development and role in nerve repair. *Cold Spring Harb. Perspect. Biol.* **2015**, *7*, 1–15. [\[CrossRef\]](#)
427. Carvalho, C.R.; Oliveira, J.M.; Reis, R.L. Modern Trends for Peripheral Nerve Repair and Regeneration: Beyond the Hollow Nerve Guidance Conduit. *Front. Bioeng. Biotechnol.* **2019**, *7*, 1–30. [\[CrossRef\]](#)
428. Evans, G.R.D.; Brandt, K.; Katz, S.; Chauvin, P.; Otto, L.; Bogle, M.; Wang, B.; Meszlenyi, R.K.; Lu, L.; Mikos, A.G.; et al. Bioactive poly(L-lactic acid) conduits seeded with Schwann cells for peripheral nerve regeneration. *Biomaterials* **2002**, *23*, 841–848. [\[CrossRef\]](#)
429. Zochodne, D.W. The challenges and beauty of peripheral nerve regrowth. *J. Peripher. Nerv. Syst.* **2012**, *17*, 1–18. [\[CrossRef\]](#)
430. Toth, C.C.; Willis, D.; Twiss, J.L.; Walsh, S.; Martinez, J.A.; Liu, W.Q.; Midha, R.; Zochodne, D.W. Locally synthesized calcitonin gene-related peptide has a critical role in peripheral nerve regeneration. *J. Neuropathol. Exp. Neurol.* **2009**, *68*, 326–337. [\[CrossRef\]](#)
431. Höke, A.; Redett, R.; Hameed, H.; Jari, R.; Zhou, C.; Li, Z.B.; Griffin, J.W.; Brushart, T.M. Schwann cells express motor and sensory phenotypes that regulate axon regeneration. *J. Neurosci.* **2006**, *26*, 9646–9655. [\[CrossRef\]](#) [\[PubMed\]](#)
432. Court, F.A.; Hendriks, W.T.J.; MacGillavry, H.D.; Alvarez, J.; Van Minnen, J. Schwann cell to axon transfer of ribosomes: Toward a novel understanding of the role of glia in the nervous system. *J. Neurosci.* **2008**, *28*, 11024–11029. [\[CrossRef\]](#) [\[PubMed\]](#)
433. Grove, M.; Kim, H.; Santerre, M.; Krupka, A.J.; Han, S.B.; Zhai, J.; Cho, J.Y.; Park, R.; Harris, M.; Kim, S.; et al. YAP/TAZ initiate and maintain Schwann cell myelination. *eLife* **2017**, *6*, 1–27. [\[CrossRef\]](#) [\[PubMed\]](#)
434. Gray, P.T.; Bevan, S.; Ritchie, J.M. High conductance anion-selective channels in rat cultured Schwann cells. *Proc. R. Soc. London. Ser. B. Biol. Sci.* **1984**, *221*, 395–409. [\[CrossRef\]](#)
435. Barres, B.A.; Chun, L.L.Y.; Corey, D.P. Ion Channels in Vertebrate Glia. *Annu. Rev. Neurosci.* **1990**, *13*, 441–474. [\[CrossRef\]](#)
436. Belin, S.; Zuloaga, K.L.; Poitelon, Y. Influence of mechanical stimuli on schwann cell biology. *Front. Cell. Neurosci.* **2017**, *11*, 1–11. [\[CrossRef\]](#)
437. Chen, Z.L.; Yu, W.M.; Strickland, S. Peripheral regeneration. *Annu. Rev. Neurosci.* **2007**, *30*, 209–233. [\[CrossRef\]](#)
438. Cattin, A.L.; Burden, J.J.; Van Emmenis, L.; MacKenzie, F.E.; Hoving, J.J.A.; Garcia Calavia, N.; Guo, Y.; McLaughlin, M.; Rosenberg, L.H.; Quereda, V.; et al. Macrophage-Induced Blood Vessels Guide Schwann Cell-Mediated Regeneration of Peripheral Nerves. *Cell* **2015**, *162*, 1127–1139. [\[CrossRef\]](#)
439. Andreone, B.J.; Lacoste, B.; Gu, C. Neuronal and Vascular Interactions. *Annu. Rev. Neurosci.* **2015**, *38*, 25–46. [\[CrossRef\]](#)
440. Muratori, L.; Gnani, S.; Fregnan, F.; Mancardi, A.; Raimondo, S.; Perroteau, I.; Geuna, S. Evaluation of Vascular Endothelial Growth Factor (VEGF) and Its Family Member Expression After Peripheral Nerve Regeneration and Denervation. *Anat. Rec.* **2018**, *301*, 1646–1656. [\[CrossRef\]](#)
441. Nakamura, T.; Mizuno, S. The discovery of Hepatocyte Growth Factor (HGF) and its significance for cell biology, life sciences and clinical medicine. *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.* **2010**, *86*, 588–610. [\[CrossRef\]](#) [\[PubMed\]](#)
442. Ko, K.R.; Lee, J.; Lee, D.; Nho, B.; Kim, S. Hepatocyte Growth Factor (HGF) Promotes Peripheral Nerve Regeneration by Activating Repair Schwann Cells. *Sci. Rep.* **2018**, *8*, 1–14. [\[CrossRef\]](#) [\[PubMed\]](#)
443. Hromada, C.; Hartmann, J.; Oesterreicher, J.; Stoiber, A.; Daerr, A.; Schädli, B.; Priglinger, E.; Teuschl-Woller, A.H.; Holnthoner, W.; Heinzel, J.; et al. Occurrence of Lymphangiogenesis in Peripheral Nerve Autografts Contrasts Schwann Cell-Induced Apoptosis of Lymphatic Endothelial Cells In Vitro. *Biomolecules* **2022**, *12*, 820. [\[CrossRef\]](#) [\[PubMed\]](#)
444. Cook, S.P.; McCleskey, E.W. Cell damage excites nociceptors through release of cytosolic ATP. *Pain* **2002**, *95*, 41–47. [\[CrossRef\]](#) [\[PubMed\]](#)

445. Hou, Q.; Barr, T.; Gee, L.; Vickers, J.; Wymer, J.; Borsani, E.; Rodella, L.; Getsios, S.; Burdo, T.; Eisenberg, E.; et al. Keratinocyte expression of calcitonin gene-related peptide β : Implications for neuropathic and inflammatory pain mechanisms. *Pain* **2011**, *152*, 2036–2051. [[CrossRef](#)]
446. Bigliardi-Qi, M.; Sumanovski, L.T.; Büchner, S.; Rufli, T.; Bigliardi, P.L. Mu-Opiate Receptor and Beta-Endorphin Expression in Nerve Endings and Keratinocytes in Human Skin. *Dermatology* **2004**, *209*, 183–189. [[CrossRef](#)] [[PubMed](#)]
447. Imokawa, G.; Yada, Y.; Miyagishi, M. Endothelins secreted from human keratinocytes are intrinsic mitogens for human melanocytes. *J. Biol. Chem.* **1992**, *267*, 24675–24680. [[CrossRef](#)]
448. Pincelli, C.; Sevnigani, C.; Manfredini, R.; Grande, A.; Fantini, F.; Bracci-Laudiero, L.; Aloe, L.; Ferrari, S.; Cossarizza, A.; Giannetti, A. Expression and function of nerve growth factor and nerve growth factor receptor on cultured keratinocytes. *J. Invest. Dermatol.* **1994**, *103*, 13–18. [[CrossRef](#)]
449. Shi, X.; Wang, L.; Clark, J.D.; Kingery, W.S. Keratinocytes express cytokines and nerve growth factor in response to neuropeptide activation of the ERK1/2 and JNK MAPK transcription pathways. *Regul. Pept.* **2013**, *186*, 92–103. [[CrossRef](#)]
450. Chateau, Y.; Misery, L. Connections between nerve endings and epidermal cells: Are they synapses? *Exp. Dermatol.* **2004**, *13*, 2–4. [[CrossRef](#)]
451. Talagas, M.; Lebonvallet, N.; Leschiera, R.; Elies, P.; Marcorelles, P.; Misery, L. Intra-epidermal nerve endings progress within keratinocyte cytoplasmic tunnels in normal human skin. *Exp. Dermatol.* **2020**, *29*, 387–392. [[CrossRef](#)]
452. Talagas, M.; Lebonvallet, N.; Leschiera, R.; Siquin, G.; Elies, P.; Haftek, M.; Pennec, J.P.; Ressenkoff, D.; La Padula, V.; Le Garrec, R.; et al. Keratinocytes Communicate with Sensory Neurons via Synaptic-like Contacts. *Ann. Neurol.* **2020**, *88*, 1205–1219. [[CrossRef](#)]
453. Zhang, R.; Zhang, Y.; Yi, S. Identification of critical growth factors for peripheral nerve regeneration. *RSC Adv.* **2019**, *9*, 10760–10765. [[CrossRef](#)]
454. Freidin, M.; Asche, S.; Bargiello, T.A.; Bennett, M.V.L.; Abrams, C.K. Connexin 32 increases the proliferative response of Schwann cells to neuregulin-1 (Nrg1). *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 3567–3572. [[CrossRef](#)]
455. Lin, G.; Zhang, H.; Sun, F.; Lu, Z.; Reed-Maldonado, A.; Lee, Y.C.; Wang, G.; Banie, L.; Lue, T.F. Brain-derived neurotrophic factor promotes nerve regeneration by activating the JAK/STAT pathway in Schwann cells. *Transl. Androl. Urol.* **2016**, *5*, 167–175. [[CrossRef](#)]
456. Shakhbazov, A.; Kawasoe, J.; Hoyng, S.A.; Kumar, R.; van Minnen, J.; Verhaagen, J.; Midha, R. Early regenerative effects of NGF-transduced Schwann cells in peripheral nerve repair. *Mol. Cell. Neurosci.* **2012**, *50*, 103–112. [[CrossRef](#)]
457. Mamet, J.; Lazdunski, M.; Voilley, N. How nerve growth factor drives physiological and inflammatory expressions of acid-sensing ion channel 3 in sensory neurons. *J. Biol. Chem.* **2003**, *278*, 48907–48913. [[CrossRef](#)]
458. Xu, P.; Rosen, K.M.; Hedstrom, K.; Rey, O.; Guha, S.; Hart, C.; Corfas, G. Nerve injury induces glial cell line-derived neurotrophic factor (GDNF) expression in schwann cells through purinergic signaling and the PKC-PKD pathway. *Glia* **2013**, *61*, 1029–1040. [[CrossRef](#)]
459. Maisonpierre, P.C.; Belluscio, L.; Squinto, S.; Ip, N.; Furth, M.E.; Lindsay, R.M.; Yancopoulos, G.D. Neurotrophin-3 : Related to Neurotrophic Factor. *Science* **1990**, *247*, 1446–1451. [[CrossRef](#)]
460. Mendell, L.M.; Johnson, R.D.; Munson, J.B. Neurotrophin modulation of the monosynaptic reflex after peripheral nerve transection. *J. Neurosci.* **1999**, *19*, 3162–3170. [[CrossRef](#)]
461. Sahenk, Z.; Nagaraja, H.N.; Mccracken, B.S.; King, W.M.; Freimer, M.L.; Cedarbaum, J.M.; Mendell, J.R. NT-3 promotes nerve regeneration and sensory improvement in CMT1A mouse models and in patients. *Neurology* **2005**, *65*, 681–689. [[CrossRef](#)] [[PubMed](#)]
462. Wiatrak, B.; Kubis-Kubiak, A.; Piwowar, A.; Barg, E. PC12 Cell Line: Cell Types, Coating of Culture Vessels, Differentiation and Other Culture Conditions. *Cells* **2020**, *9*, 958. [[CrossRef](#)] [[PubMed](#)]
463. Ning, N.; Hu, J.F.; Yuan, Y.H.; Zhang, X.Y.; Dai, J.G.; Chen, N.H. Huperzine A derivative M3 protects PC12 cells against sodium nitroprusside-induced apoptosis. *Acta Pharmacol. Sin.* **2012**, *33*, 34–40. [[CrossRef](#)] [[PubMed](#)]
464. Koser, D.E.; Thompson, A.J.; Foster, S.K.; Dwivedy, A.; Pillai, E.K.; Sheridan, G.K.; Svoboda, H.; Viana, M.; Costa, L.D.F.; Guck, J.; et al. Mechanosensing is critical for axon growth in the developing brain. *Nat. Neurosci.* **2016**, *19*, 1592–1598. [[CrossRef](#)] [[PubMed](#)]
465. Bray, D. Axonal growth in response to experimentally applied mechanical tension. *Dev. Biol.* **1984**, *102*, 379–389. [[CrossRef](#)]
466. Kerstein, P.C.; Nichol, R.H.; Gomez, T.M. Mechanochemical regulation of growth cone motility. *Front. Cell. Neurosci.* **2015**, *9*, 1–16. [[CrossRef](#)]
467. Weiss, P. Nerve patterns: The mechanics of nerve growth. *Growth: Third Growth Symp.* **1941**, *5*, 163–203. [[CrossRef](#)]
468. Li, F.; Lo, T.Y.; Miles, L.; Wang, Q.; Noristani, H.N.; Li, D.; Niu, J.; Trombley, S.; Goldshteyn, J.I.; Wang, C.; et al. The Atr-Chek1 pathway inhibits axon regeneration in response to Piezo-dependent mechanosensation. *Nat. Commun.* **2021**, *12*, 1–20. [[CrossRef](#)]
469. Moreno-López, B. Local isoform-specific NOS inhibition: A promising approach to promote motor function recovery after nerve injury. *J. Neurosci. Res.* **2010**, *88*, 1846–1857. [[CrossRef](#)]
470. Zhou, S.; Shen, D.; Wang, Y.; Gong, L.; Tang, X.; Yu, B.; Gu, X.; Ding, F. microRNA-222 Targeting PTEN Promotes Neurite Outgrowth from Adult Dorsal Root Ganglion Neurons following Sciatic Nerve Transection. *PLoS ONE* **2012**, *7*, e44768. [[CrossRef](#)]

471. Arthur-Farraj, P.J.; Morgan, C.C.; Adamowicz, M.; Gomez-Sanchez, J.A.; Fazal, S.V.; Beucher, A.; Razzaghi, B.; Mirsky, R.; Jessen, K.R.; Aitman, T.J. Changes in the Coding and Non-coding Transcriptome and DNA Methylome that Define the Schwann Cell Repair Phenotype after Nerve Injury. *Cell Rep.* **2017**, *20*, 2719–2734. [[CrossRef](#)]
472. Chang, W.; Kanda, H.; Ikeda, R.; Ling, J.; DeBerry, J.J.; Gu, J.G. Merkel disc is a serotonergic synapse in the epidermis for transmitting tactile signals in mammals. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, E5491–E5500. [[CrossRef](#)]
473. Borger, A.; Stadlmayr, S.; Haertinger, M.; Semmler, L.; Supper, P.; Millesi, F.; Radtke, C. How miRNAs Regulate Schwann Cells during Peripheral Nerve Regeneration—A Systemic Review. *Int. J. Mol. Sci.* **2022**, *23*, 3440. [[CrossRef](#)]
474. Hussein, M.; Magdy, R. MicroRNAs in central nervous system disorders: Current advances in pathogenesis and treatment. *Egypt. J. Neurol. Psychiatry Neurosurg.* **2021**, *57*, 1–11. [[CrossRef](#)]
475. Wang, X.; Chen, Q.; Yi, S.; Liu, Q.; Zhang, R.; Wang, P.; Qian, T.; Li, S. The microRNAs let-7 and miR-9 down-regulate the axon-guidance genes Ntn1 and Dcc during peripheral nerve regeneration. *J. Biol. Chem.* **2019**, *294*, 3489–3500. [[CrossRef](#)]
476. Yi, S.; Yuan, Y.; Chen, Q.; Wang, X.; Gong, L.; Liu, J.; Gu, X.; Li, S. Regulation of Schwann cell proliferation and migration by MIR-1 targeting brain-derived neurotrophic factor after peripheral nerve injury. *Sci. Rep.* **2016**, *6*, 1–10. [[CrossRef](#)]
477. Liu, Y.P.; Xu, P.; Guo, C.X.; Luo, Z.R.; Zhu, J.; Mou, F.F.; Cai, H.; Wang, C.; Ye, X.C.; Shao, S.J.; et al. miR-1b overexpression suppressed proliferation and migration of RSC96 and increased cell apoptosis. *Neurosci. Lett.* **2018**, *687*, 137–145. [[CrossRef](#)]
478. Li, X.; Yuan, L.; Wang, J.; Zhang, Z.; Fu, S.; Wang, S.; Li, X. MiR-1b up-regulation inhibits rat neuron proliferation and regeneration yet promotes apoptosis via targeting KLF7. *Folia Neuropathol.* **2021**, *59*, 67–80. [[CrossRef](#)]
479. Zhou, S.; Gao, R.; Hu, W.; Qian, T.; Wang, N.; Ding, G.; Ding, F.; Yu, B.; Gu, X. MiR-9 inhibits schwann cell migration by targeting cthrc1 following sciatic nerve injury. *J. Cell Sci.* **2014**, *127*, 967–976. [[CrossRef](#)]
480. Li, S.; Wang, X.; Gu, Y.; Chen, C.; Wang, Y.; Liu, J.; Hu, W.; Yu, B.; Wang, Y.; Ding, F.; et al. Let-7 microRNAs regenerate peripheral nerve regeneration by targeting nerve growth factor. *Mol. Ther.* **2015**, *23*, 423–433. [[CrossRef](#)]
481. Gökbuget, D.; Pereira, J.A.; Bachofner, S.; Marchais, A.; Ciaudo, C.; Stoffel, M.; Schulte, J.H.; Suter, U. The Lin28/let-7 axis is critical for myelination in the peripheral nervous system. *Nat. Commun.* **2015**, *6*. [[CrossRef](#)] [[PubMed](#)]
482. Ning, X.J.; Lu, X.H.; Luo, J.C.; Chen, C.; Gao, Q.; Li, Z.Y.; Wang, H. Molecular mechanism of microRNA-21 promoting Schwann cell proliferation and axon regeneration during injured nerve repair. *RNA Biol.* **2020**, *17*, 1508–1519. [[CrossRef](#)] [[PubMed](#)]
483. López-Leal, R.; Díaz-Viraqué, F.; Catalán, R.J.; Saquel, C.; Enright, A.; Iraola, G.; Court, F.A. Schwann cell reprogramming into repair cells increases miRNA-21 expression in exosomes promoting axonal growth. *J. Cell Sci.* **2020**, *133*, jcs239004. [[CrossRef](#)] [[PubMed](#)]
484. Yi, S.; Wang, Q.H.; Zhao, L.L.; Qin, J.; Wang, Y.X.; Yu, B.; Zhou, S.L. MiR-30c promotes Schwann cell remyelination following peripheral nerve injury. *Neural Regen. Res.* **2017**, *12*, 1708–1714. [[CrossRef](#)] [[PubMed](#)]
485. Zou, D.; Zhou, X.; Liu, J.; Zhao, Y.; Jiang, X. MiR-34a regulates Schwann cell proliferation and migration by targeting CNTN2. *NeuroReport* **2020**, *31*, 1180–1188. [[CrossRef](#)]
486. Viader, A.; Chang, L.W.; Fahrner, T.; Nagarajan, R.; Milbrandt, J. MicroRNAs modulate schwann cell response to nerve injury by reinforcing transcriptional silencing of dedifferentiation-related genes. *J. Neurosci.* **2011**, *31*, 17358–17369. [[CrossRef](#)]
487. Nagata, K.; Hama, I.; Kiryu-Seo, S.; Kiyama, H. MicroRNA-124 is down regulated in nerve-injured motor neurons and it potentially targets mRNAs for KLF6 and STAT3. *Neuroscience* **2014**, *256*, 426–432. [[CrossRef](#)]
488. Zhu, H.; Xue, C.; Yao, M.; Wang, H.; Zhang, P.; Qian, T.; Zhou, S.; Li, S.; Yu, B.; Wang, Y.; et al. MIR-129 controls axonal regeneration via regulating insulin-like growth factor-1 in peripheral nerve injury. *Cell Death Dis.* **2018**, *9*, 1–17. [[CrossRef](#)]
489. Yao, C.; Shi, X.; Zhang, Z.; Zhou, S.; Qian, T.; Wang, Y.; Ding, F.; Gu, X.; Yu, B. Hypoxia-Induced Upregulation of miR-132 Promotes Schwann Cell Migration After Sciatic Nerve Injury by Targeting PRKAG3. *Mol. Neurobiol.* **2016**, *53*, 5129–5139. [[CrossRef](#)]
490. Sullivan, T.; Robert, L.; Teebagy, P.; Morgan, S.; Beatty, E.; Cicuto, B.; Nowd, P.; Rieger-Christ, K.M.; Bryan, D. Spatiotemporal microRNA profile in peripheral nerve regeneration: MiR-138 targets vimentin and inhibits Schwann cell migration and proliferation. *Neural Regen. Res.* **2018**, *13*, 1253–1262. [[CrossRef](#)]
491. Li, W.Y.; Zhang, W.T.; Cheng, Y.X.; Liu, Y.C.; Zhai, F.G.; Sun, P.; Li, H.T.; Deng, L.X.; Zhu, X.F.; Wang, Y. Inhibition of KLF7-Targeting MicroRNA 146b Promotes Sciatic Nerve Regeneration. *Neurosci. Bull.* **2018**, *34*, 419–437. [[CrossRef](#)]
492. Yu, B.; Zhou, S.; Wang, Y.; Qian, T.; Ding, G.; Ding, F.; Gu, X. Mir-221 and mir-222 promote Schwann cell proliferation and migration by targeting LASS2 after sciatic nerve injury. *J. Cell Sci.* **2012**, *125*, 2675–2683. [[CrossRef](#)]
493. Liu, X.; Cui, X.; Guan, G.; Dong, Y.; Zhang, Z. microRNA-192-5p is involved in nerve repair in rats with peripheral nerve injury by regulating XIAP. *Cell Cycle* **2020**, *19*, 326–338. [[CrossRef](#)]
494. Zhang, X.; Gong, X.; Qiu, J.; Zhang, Y.; Gong, F. MicroRNA-210 contributes to peripheral nerve regeneration through promoting the proliferation and migration of Schwann cells. *Exp. Ther. Med.* **2017**, *14*, 2809–2816. [[CrossRef](#)]
495. Zhao, L.; Yuan, Y.; Li, P.; Pan, J.; Qin, J.; Liu, Y.; Zhang, Y.; Tian, F.; Yu, B.; Zhou, S. miR-221-3p Inhibits Schwann Cell Myelination. *Neuroscience* **2018**, *379*, 239–245. [[CrossRef](#)]
496. Li, S.; Zhang, R.; Yuan, Y.; Yi, S.; Chen, Q.; Gong, L.; Liu, J.; Ding, F.; Cao, Z.; Gu, X. MiR-340 Regulates Fibrinolysis and Axon Regrowth Following Sciatic Nerve Injury. *Mol. Neurobiol.* **2017**, *54*, 4379–4389. [[CrossRef](#)]
497. Zhang, Z.; Li, X.; Li, A.; Wu, G. miR-485-5p suppresses Schwann cell proliferation and myelination by targeting cdc42 and Rac1. *Exp. Cell Res.* **2020**, *388*, 111803. [[CrossRef](#)]

498. Wang, P.; He, J.; Wang, S.; Wang, X.; Liu, Q.; Peng, W.; Qian, T. miR-3075 Inhibited the Migration of Schwann Cells by Targeting Cntn2. *Neurochem. Res.* **2018**, *43*, 1879–1886. [\[CrossRef\]](#)
499. Liu, Q.Y.; Miao, Y.; Wang, X.H.; Wang, P.; Cheng, Z.C.; Qian, T.M. Increased levels of miR-3099 induced by peripheral nerve injury promote Schwann cell proliferation and migration. *Neural Regen. Res.* **2019**, *14*, 525–531. [\[CrossRef\]](#)
500. Motz, C.T.; Kabat, V.; Saxena, T.; Bellamkonda, R.V.; Zhu, C. Neuromechanobiology: An Expanding Field Driven by the Force of Greater Focus. *Adv. Healthc. Mater.* **2021**, *10*, 1–25. [\[CrossRef\]](#)
501. De Vincentiis, S.; Falconieri, A.; Scribano, V.; Ghignoli, S.; Raffa, V. Manipulation of Axonal Outgrowth via Exogenous Low Forces. *Int. J. Mol. Sci.* **2020**, *21*, 8009. [\[CrossRef\]](#) [\[PubMed\]](#)
502. Fallon, J.B.; Bent, L.R.; McNulty, P.A.; Macefield, V.G. Evidence for strong synaptic coupling between single tactile afferents from the sole of the foot and motoneurons supplying leg muscles. *J. Neurophysiol.* **2005**, *94*, 3795–3804. [\[CrossRef\]](#) [\[PubMed\]](#)
503. Srinivasan, S.S.; Herr, H. A cutaneous mechanoneural interface for neuroprosthetic feedback. *Nat. Biomed. Eng.* **2021**. [\[CrossRef\]](#) [\[PubMed\]](#)
504. Mosabbir, A.; Almeida, Q.J.; Ahonen, H. The effects of long-term 40-hz physioacoustic vibrations on motor impairments in parkinson's disease: A double-blinded randomized control trial. *Healthcare* **2020**, *8*, 113. [\[CrossRef\]](#) [\[PubMed\]](#)
505. Vuong, V.; Mosabbir, A.; Paneduro, D.; Picard, L.; Faghfoury, H.; Evans, M.; Gordon, A.; Bartel, L. Effects of Rhythmic Sensory Stimulation on Ehlers-Danlos Syndrome: A Pilot Study. *Pain Res. Manag.* **2020**, *2020*, 3586767. [\[CrossRef\]](#) [\[PubMed\]](#)
506. Iaccarino, H.F.; Singer, A.C.; Martorell, A.J.; Rudenko, A.; Gao, F.; Gillingham, T.Z.; Mathys, H.; Seo, J.; Kritskiy, O.; Abdurrob, F.; et al. Gamma frequency entrainment attenuates amyloid load and modifies microglia. *Nature* **2016**, *540*, 230–235. [\[CrossRef\]](#)
507. Clements-Cortes, A.; Ahonen, H.; Evans, M.; Freedman, M.; Bartel, L. Short-Term Effects of Rhythmic Sensory Stimulation in Alzheimer's Disease: An Exploratory Pilot Study. *J. Alzheimer's Dis.* **2016**, *52*, 651–660. [\[CrossRef\]](#)
508. King, L.K.; Almeida, Q.J.; Ahonen, H. Short-term effects of vibration therapy on motor impairments in Parkinson's disease. *NeuroRehabilitation* **2009**, *25*, 297–306. [\[CrossRef\]](#)
509. Wolf, E.J.; Cruz, T.H.; Emondi, A.A.; Langhals, N.B.; Naufel, S.; Peng, G.C.; Schulz, B.W.; Wolfson, M. Advanced technologies for intuitive control and sensation of prosthetics. *Biomed. Eng. Lett.* **2020**, *10*, 119–128. [\[CrossRef\]](#)
510. Botvinick, M.; Cohen, J.D. Rubber hand 'feels' what eyes see. *Nature* **1998**, *391*, 756. [\[CrossRef\]](#)
511. Jones, L.A. Motor illusions: What do they reveal about proprioception? *Psychol. Bull.* **1988**, *103*, 72–86. [\[CrossRef\]](#)
512. Synofzik, M.; Vosgerau, G.; Newen, A. I move, therefore I am: A new theoretical framework to investigate agency and ownership. *Conscious. Cogn.* **2008**, *17*, 411–424. [\[CrossRef\]](#)
513. Beauchamp, M.S.; Yasar, N.E.; Kishan, N.; Ro, T. Human MST but not MT responds to tactile stimulation. *J. Neurosci.* **2007**, *27*, 8261–8267. [\[CrossRef\]](#) [\[PubMed\]](#)
514. Blake, D.T.; Hsiao, S.S.; Johnson, K.O. Neural coding mechanisms in tactile pattern recognition: The relative contributions of slowly and rapidly adapting mechanoreceptors to perceived roughness. *J. Neurosci.* **1997**, *17*, 7480–7489. [\[CrossRef\]](#) [\[PubMed\]](#)
515. Hagen, M.C.; Franzén, O.; McGlone, F.; Essick, G.; Dancer, C.; Pardo, J.V. Tactile motion activates the human middle temporal/V5 (MT/V5) complex. *Eur. J. Neurosci.* **2002**, *16*, 957–964. [\[CrossRef\]](#) [\[PubMed\]](#)
516. Ernst, M.O.; Banks, M.S. Humans integrate visual and haptic information in a statistically optimal fashion. *Nature* **2002**, *415*, 429–433. [\[CrossRef\]](#)
517. Van Den Bos, E.; Jeannerod, M. Sense of body and sense of action both contribute to self-recognition. *Cognition* **2002**, *85*, 177–187. [\[CrossRef\]](#)
518. Kalckert, A.; Henrik Ehrsson, H. Moving a rubber hand that feels like your own: A dissociation of ownership and agency. *Front. Hum. Neurosci.* **2012**, *6*, 1–14. [\[CrossRef\]](#)
519. Rognini, G.; Petrini, F.M.; Raspopovic, S.; Valle, G.; Granata, G.; Strauss, I.; Solcà, M.; Bello-Ruiz, J.; Herbelin, B.; Mange, R.; et al. Multisensory bionic limb to achieve prosthesis embodiment and reduce distorted phantom limb perceptions. *J. Neurol. Neurosurg. Psychiatry* **2019**, *90*, 833–836. [\[CrossRef\]](#)
520. Hill, A. Phantom limb pain: A review of the literature on attributes and potential mechanisms. *J. Pain Symptom Manag.* **1999**, *17*, 125–142. [\[CrossRef\]](#)
521. Alahakone, A.U.; Senanayake, S.M.N.A. Vibrotactile feedback systems: Current trends in rehabilitation, sports and information display. In Proceedings of the 2009 IEEE/ASME International Conference on Advanced Intelligent Mechatronics, Singapore, 14–17 July 2009; pp. 1148–1153. [\[CrossRef\]](#)
522. Bramati, I.E.; Rodrigues, E.C.; Simões, E.L.; Melo, B.; Höfle, S.; Moll, J.; Lent, R.; Tovar-Moll, F. Lower limb amputees undergo long-distance plasticity in sensorimotor functional connectivity. *Sci. Rep.* **2019**, *9*, 1–10. [\[CrossRef\]](#)
523. Kaas, J.H.; Nelson, R.J.; Sur, M.; Dykes, R.W.; Merzenich, M.M. The somatotopic organization of the ventroposterior thalamus of the squirrel monkey, *Saimiri sciureus*. *J. Comp. Neurol.* **1984**, *226*, 111–140. [\[CrossRef\]](#)
524. Ackerley, R.; Hassan, E.; Curran, A.; Wessberg, J.; Olausson, H.; McGlone, F. An fMRI study on cortical responses during active self-touch and passive touch from others. *Front. Behav. Neurosci.* **2012**, *6*, 1–9. [\[CrossRef\]](#)
525. Disbrow, E.; Roberts, T.; Krubitzer, L. Somatotopic organization of cortical fields in the lateral sulcus of *Homo sapiens*: Evidence for SII and PV. *J. Comp. Neurol.* **2000**, *418*, 1–21. [\[CrossRef\]](#)
526. Francis, S.T.; Kelly, E.F.; Bowtell, R.; Dunseath, W.J.R.; Folger, S.E.; McGlone, F. fMRI of the responses to vibratory stimulation of digit tips. *NeuroImage* **2000**, *11*, 188–202. [\[CrossRef\]](#)

527. Ruben, J.; Schwiemann, J.; Deuchert, M.; Meyer, R.; Krause, T.; Curio, G.; Villringer, K.; Kurth, R.; Villringer, A. Somatotopic organization of human secondary somatosensory cortex. *Cereb. Cortex* **2001**, *11*, 463–473. [\[CrossRef\]](#)
528. Penfield, W.; Boldrey, E. Somatic Motor And Sensory Representation In The Cerebral Cortex Of Man As Studied By Electrical Stimulation. *Brain* **1937**, *60*, 389–443. [\[CrossRef\]](#)
529. Llinás, R.R.; Ribary, U.; Jeanmonod, D.; Kronberg, E.; Mitra, P.P. Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 15222–15227. [\[CrossRef\]](#) [\[PubMed\]](#)
530. Hara, E.S.; Witzel, A.L.; de Luca, C.E.P.; Ballester, R.Y.; Kuboki, T.; Bolzan, M.C. A novel vibratory stimulation-based occlusal splint for alleviation of TMD painful symptoms: A pilot study. *J. Oral Rehabil.* **2013**, *40*, 179–184. [\[CrossRef\]](#) [\[PubMed\]](#)
531. Roy, E.A.; Hollins, M.; Maixner, W. Reduction of TMD pain by high-frequency vibration: A spatial and temporal analysis. *Pain* **2003**, *101*, 267–274. [\[CrossRef\]](#)
532. List, E.B.; Krijgh, D.D.; Martin, E.; Coert, J.H. Prevalence of residual limb pain and symptomatic neuromas after lower extremity amputation: A systematic review and meta-analysis. *Pain* **2021**, *162*, 1906–1913. [\[CrossRef\]](#)
533. Meade, Z.S.; Likens, A.D.; Kent, J.A.; Takahashi, K.Z.; Wurdeman, S.R.; Jacobsen, A.L.; Hernandez, M.E.; Stergiou, N. Subthreshold Vibration Influences Standing Balance but Has Unclear Impact on Somatosensation in Persons With Transtibial Amputations. *Front. Physiol.* **2022**, *13*, 1–12. [\[CrossRef\]](#)
534. Cochrane, D.J.; Cochrane, F.; Roake, J.A. An exploratory study of vibration therapy on muscle function in patients with peripheral artery disease. *J. Vasc. Surg.* **2020**, *71*, 1340–1345. [\[CrossRef\]](#)
535. Rodríguez-Pérez, M.P.; Sánchez-Herrera-Baeza, P.; Cano-de-la Cuerda, R.; Camacho-Montaña, L.R.; Serrada-Tejeda, S.; Pérez-de Heredia-Torres, M. Effects of Intensive Vibratory Treatment with a Robotic System on the Recovery of Sensation and Function in Patients with Subacute and Chronic Stroke: A Non-Randomized Clinical Trial. *J. Clin. Med.* **2022**, *11*, 3572. [\[CrossRef\]](#)
536. Sainburg, R.L.; Ghilardi, M.F.; Poizner, H.; Ghez, C. Control of limb dynamics in normal subjects and patients without proprioception. *J. Neurophysiol.* **1995**, *73*, 820–835. [\[CrossRef\]](#)
537. Resnik, L.; Meucci, M.R.; Lieberman-Klinger, S.; Fantini, C.; Kelty, D.L.; Disla, R.; Sasson, N. Advanced upper limb prosthetic devices: Implications for upper limb prosthetic rehabilitation. *Arch. Phys. Med. Rehabil.* **2012**, *93*, 710–717. [\[CrossRef\]](#)
538. Graczyk, E.L.; Resnik, L.; Schiefer, M.A.; Schmitt, M.S.; Tyler, D.J. Home use of a neural-connected sensory prosthesis provides the functional and psychosocial experience of having a hand again. *Sci. Rep.* **2018**, *8*, 1–17. [\[CrossRef\]](#)
539. Biddiss, E.; Chau, T. Upper-limb prosthetics: Critical factors in device abandonment. *Am. J. Phys. Med. Rehabil.* **2007**, *86*, 977–987. [\[CrossRef\]](#)
540. Petrini, F.M.; Bumbasirevic, M.; Valle, G.; Ilic, V.; Mijović, P.; Čvančara, P.; Barberi, F.; Katic, N.; Bortolotti, D.; Andreu, D.; et al. Sensory feedback restoration in leg amputees improves walking speed, metabolic cost and phantom pain. *Nat. Med.* **2019**, *25*, 1356–1363. [\[CrossRef\]](#)
541. Raspopovic, S.; Capogrosso, M.; Petrini, F.M.; Bonizzato, M.; Rigosa, J.; Di Pino, G.; Carpaneto, J.; Controzzi, M.; Boretius, T.; Fernandez, E.; et al. Restoring Natural Sensory Feedback in Real-Time Bidirectional Hand Prostheses. *Sci. Transl. Med.* **2014**, *6*, 222ra19. [\[CrossRef\]](#)
542. Oddo, C.M.; Raspopovic, S.; Artoni, F.; Mazzoni, A.; Spigler, G.; Petrini, F.; Giambattistelli, F.; Vecchio, F.; Miraglia, F.; Zollo, L.; et al. Intraneural stimulation elicits discrimination of textural features by artificial fingertip in intact and amputee humans. *eLife* **2016**, *5*, 1–27. [\[CrossRef\]](#) [\[PubMed\]](#)
543. Osborn, L.E.; Dragomir, A.; Betthausen, J.L.; Hunt, C.L.; Nguyen, H.H.; Kaliki, R.R.; Thakor, N.V. Prosthesis with neuromorphic multilayered e-dermis perceives touch and pain. *Sci. Robot.* **2018**, *3*, 1–12. [\[CrossRef\]](#) [\[PubMed\]](#)
544. Valle, G.; Mazzoni, A.; Iberite, F.; D’Anna, E.; Strauss, I.; Granata, G.; Controzzi, M.; Clemente, F.; Rognini, G.; Cipriani, C.; et al. Biomimetic Intraneural Sensory Feedback Enhances Sensation Naturalness, Tactile Sensitivity, and Manual Dexterity in a Bidirectional Prosthesis. *Neuron* **2018**, *100*, 37–45.e7. [\[CrossRef\]](#) [\[PubMed\]](#)
545. George, J.A.; Kluger, D.T.; Davis, T.S.; Wendelken, S.M.; Okorokova, E.V.; He, Q.; Duncan, C.C.; Hutchinson, D.T.; Thumser, Z.C.; Beckler, D.T.; et al. Biomimetic sensory feedback through peripheral nerve stimulation improves dexterous use of a bionic hand. *Sci. Robot.* **2019**, *4*, 1–12. [\[CrossRef\]](#) [\[PubMed\]](#)
546. Tan, D.W.; Schiefer, M.A.; Keith, M.W.; Anderson, J.R.; Tyler, J.; Tyler, D.J. A neural interface provides long-term stable natural touch perception. *Sci. Transl. Med.* **2014**, *6*, 257ra138. [\[CrossRef\]](#)
547. Oddsson, L.I.E.; Bisson, T.; Cohen, H.S.; Jacobs, L.; Khoshnoodi, M.; Kung, D.; Lipsitz, L.A.; Manor, B.; McCracken, P.; Rumsey, Y.; et al. The Effects of a Wearable Sensory Prosthesis on Gait and Balance Function After 10 Weeks of Use in Persons with Peripheral Neuropathy and High Fall Risk—The Walk2Wellness Trial. *Front. Aging Neurosci.* **2020**, *12*, 1–21. [\[CrossRef\]](#)
548. Koehler-McNicholas, S.R.; Danzl, L.; Cataldo, A.Y.; Oddsson, L.I.E. Neuromodulation to improve gait and balance function using a sensory neuroprosthesis in people who report insensate feet—A randomized control crossover study. *PLoS ONE* **2019**, *14*, e216212. [\[CrossRef\]](#)
549. Ortiz-Catalan, M.; Håkansson, B.; Brånemark, R. An osseointegrated human-machine gateway for long-term sensory feedback and motor control of artificial limbs. *Sci. Transl. Med.* **2014**, *6*, 257re6. [\[CrossRef\]](#)
550. Page, D.M.; George, J.A.; Kluger, D.T.; Duncan, C.; Wendelken, S.; Davis, T.; Hutchinson, D.T.; Clark, G.A. Motor Control and Sensory Feedback Enhance Prosthesis Embodiment and Reduce Phantom Pain After Long-Term Hand Amputation. *Front. Hum. Neurosci.* **2018**, *12*, 1–16. [\[CrossRef\]](#)

551. Clippinger, F.W.; Avery, R.; Titus, B.R. A sensory feedback system for an upper-limb amputation prosthesis. *Bull. Prosthetics Res.* **1974**, *1974*, 247–258.
552. Clippinger, F.W.; Seaber, A.V.; McElhaney, J.H.; Harrelson, J.M.; Maxwell, G.M. Afferent sensory feedback for lower extremity prosthesis. *Clin. Orthop. Relat. Res.* **1982**, *169*, 202–208. [\[CrossRef\]](#)
553. Markovic, M.; Schweisfurth, M.A.; Engels, L.F.; Bentz, T.; Wüstefeld, D.; Farina, D.; Dosen, S. The clinical relevance of advanced artificial feedback in the control of a multi-functional myoelectric prosthesis. *J. NeuroEngineering Rehabil.* **2018**, *15*, 28. [\[CrossRef\]](#)
554. Wendelken, S.; Page, D.M.; Davis, T.; Wark, H.A.C.; Kluger, D.T.; Duncan, C.; Warren, D.J.; Hutchinson, D.T.; Clark, G.A. Restoration of motor control and proprioceptive and cutaneous sensation in humans with prior upper-limb amputation via multiple Utah Slanted Electrode Arrays (USEAs) implanted in residual peripheral arm nerves. *J. NeuroEngineering Rehabil.* **2017**, *14*, 1–17. [\[CrossRef\]](#)
555. Schiefer, M.; Tan, D.; Sidek, S.M.; Tyler, D.J. Sensory feedback by peripheral nerve stimulation improves task performance in individuals with upper limb loss using a myoelectric prosthesis. *J. Neural Eng.* **2016**, *13*, 016001. [\[CrossRef\]](#)
556. Osborn, L.E.; Ding, K.; Hays, M.A.; Bose, R.; Iskarous, M.M.; Dragomir, A.; Tayeb, Z.; Lévy, G.M.; Hunt, C.L.; Cheng, G.; et al. Sensory stimulation enhances phantom limb perception and movement decoding. *J. Neural Eng.* **2020**, *17*, 056006. [\[CrossRef\]](#)
557. Schultz, A.E.; Marasco, P.D.; Kuiken, T.A. Vibrotactile detection thresholds for chest skin of amputees following targeted reinnervation surgery. *Brain Res.* **2009**, *1251*, 121–129. [\[CrossRef\]](#)
558. Marasco, P.D.; Schultz, A.E.; Kuiken, T.A. Sensory capacity of reinnervated skin after redirection of amputated upper limb nerves to the chest. *Brain* **2009**, *132*, 1441–1448. [\[CrossRef\]](#)
559. Hebert, J.S.; Chan, K.M.; Dawson, M.R. Cutaneous sensory outcomes from three transhumeral targeted reinnervation cases. *Prosthetics Orthot. Int.* **2016**, *40*, 303–310. [\[CrossRef\]](#)
560. Hebert, J.S.; Olson, J.L.; Morhart, M.J.; Dawson, M.R.; Marasco, P.D.; Kuiken, T.A.; Chan, K.M. Novel targeted sensory reinnervation technique to restore functional hand sensation after transhumeral amputation. *IEEE Trans. Neural Syst. Rehabil. Eng.* **2014**, *22*, 765–773. [\[CrossRef\]](#)
561. Marasco, P.D.; Kim, K.; Colgate, J.E.; Peshkin, M.A.; Kuiken, T.A. Robotic touch shifts perception of embodiment to a prosthesis in targeted reinnervation amputees. *Brain* **2011**, *134*, 747–758. [\[CrossRef\]](#)
562. Hebert, J.S.; Elzinga, K.; Chan, K.M.; Olson, J.; Morhart, M. Updates in Targeted Sensory Reinnervation for Upper Limb Amputation. *Curr. Surg. Rep.* **2014**, *2*, 1–9. [\[CrossRef\]](#)
563. Marasco, P.D.; Hebert, J.S.; Sensinger, J.W.; Beckler, D.T.; Thumser, Z.C.; Shehata, A.W.; Williams, H.E.; Wilson, K.R. Neurorobotic fusion of prosthetic touch, kinesthesia, and movement in bionic upper limbs promotes intrinsic brain behaviors. *Sci. Robot.* **2021**, *6*, abf3368. [\[CrossRef\]](#) [\[PubMed\]](#)
564. Gardetto, A.; Baur, E.M.; Prahm, C.; Smekal, V.; Jeschke, J.; Peterzell, G.; Pedrini, M.T.; Kolbenschlag, J. Reduction of phantom limb pain and improved proprioception through a tsr-based surgical technique: A case series of four patients with lower limb amputation. *J. Clin. Med.* **2021**, *10*, 4029. [\[CrossRef\]](#) [\[PubMed\]](#)
565. Granata, G.; Di Iorio, R.; Miraglia, F.; Caulo, M.; Iodice, F.; Vecchio, F.; Valle, G.; Strauss, I.; D’Anna, E.; Iberite, F.; et al. Brain reactions to the use of sensorized hand prosthesis in amputees. *Brain Behav.* **2020**, *10*, 1–12. [\[CrossRef\]](#)
566. Dietrich, C.; Walter-Walsh, K.; Preißler, S.; Hofmann, G.O.; Witte, O.W.; Miltner, W.H.R.; Weiss, T. Sensory feedback prosthesis reduces phantom limb pain: Proof of a principle. *Neurosci. Lett.* **2012**, *507*, 97–100. [\[CrossRef\]](#)
567. Serino, A.; Akseilrod, M.; Salomon, R.; Martuzzi, R.; Blefari, M.L.; Canzoneri, E.; Rognini, G.; Van Der Zwaag, W.; Iakova, M.; Luthi, F.; et al. Upper limb cortical maps in amputees with targeted muscle and sensory reinnervation. *Brain* **2017**, *140*, 2993–3011. [\[CrossRef\]](#)
568. Dietrich, C.; Nehrlich, S.; Seifert, S.; Blume, K.R.; Miltner, W.H.R.; Hofmann, G.O.; Weiss, T. Leg prosthesis with somatosensory feedback reduces phantom limb pain and increases functionality. *Front. Neurol.* **2018**, *9*, 1–10. [\[CrossRef\]](#)
569. Münte, T.F.; Jöbges, E.M.; Wieringa, B.M.; Klein, S.; Schubert, M.; Johannes, S.; Dengler, R. Human evoked potentials to long duration vibratory stimuli: Role of muscle afferents. *Neurosci. Lett.* **1996**, *216*, 163–166. [\[CrossRef\]](#)
570. Bark, K.; Wheeler, J.W.; Premakumar, S.; Cutkosky, M.R. Comparison of skin stretch and vibrotactile stimulation for feedback of proprioceptive information. In Proceedings of the 2008 Symposium on Haptic Interfaces for Virtual Environment and Teleoperator Systems, Reno, NV, USA, 13–14 March 2008; pp. 71–78. [\[CrossRef\]](#)
571. Meyers, E.C.; Kasliwal, N.; Solorzano, B.R.; Lai, E.; Bendale, G.; Berry, A.; Ganzer, P.D.; Romero-Ortega, M.; Rennaker, R.L.; Kilgard, M.P.; et al. Enhancing plasticity in central networks improves motor and sensory recovery after nerve damage. *Nat. Commun.* **2019**, *10*, 1–14. [\[CrossRef\]](#)
572. Ganzer, P.D.; Darrow, M.J.; Meyers, E.C.; Solorzano, B.R.; Ruiz, A.D.; Robertson, N.M.; Adcock, K.S.; James, J.T.; Jeong, H.S.; Becker, A.M.; et al. Closed-loop neuromodulation restores network connectivity and motor control after spinal cord injury. *eLife* **2018**, *7*, 1–19. [\[CrossRef\]](#)
573. Meyers, E.C.; Solorzano, B.R.; James, J.; Ganzer, P.D.; Lai, E.S.; Rennaker, R.L.; Kilgard, M.P.; Hays, S.A. Vagus nerve stimulation enhances stable plasticity and generalization of stroke recovery. *Stroke* **2018**, *49*, 710–717. [\[CrossRef\]](#)
574. Porter, B.A.; Khodaparast, N.; Fayyaz, T.; Cheung, R.J.; Ahmed, S.S.; Vrana, W.A.; Rennaker, R.L.; Kilgard, M.P. Repeatedly pairing vagus nerve stimulation with a movement reorganizes primary motor cortex. *Cereb. Cortex* **2012**, *22*, 2365–2374. [\[CrossRef\]](#)
575. Engineer, N.D.; Kimberley, T.J.; Prudente, C.N.; Dawson, J.; Tarver, W.B.; Hays, S.A. Targeted vagus nerve stimulation for rehabilitation after stroke. *Front. Neurosci.* **2019**, *13*, 1–18. [\[CrossRef\]](#)

576. Darrow, M.J.; Mian, T.M.; Torres, M.; Haider, Z.; Danaphongse, T.; Rennaker, R.L.; Kilgard, M.P.; Hays, S.A. Restoration of Somatosensory Function by Pairing Vagus Nerve Stimulation with Tactile Rehabilitation. *Ann. Neurol.* **2020**, *87*, 194–205. [[CrossRef](#)]
577. Kilgard, M.P.; Rennaker, R.L.; Alexander, J.; Dawson, J. Vagus nerve stimulation paired with tactile training improved sensory function in a chronic stroke patient. *NeuroRehabilitation* **2018**, *42*, 159–165. [[CrossRef](#)]
578. Li, J.; Zhang, Q.; Li, S.; Niu, L.; Ma, J.; Wen, L.; Zhang, L.; Li, C. $\alpha 7$ nAChR mediates transcutaneous auricular vagus nerve stimulation-induced neuroprotection in a rat model of ischemic stroke by enhancing axonal plasticity. *Neurosci. Lett.* **2020**, *730*, 135031. [[CrossRef](#)]
579. Lu, X.X.; Hong, Z.Q.; Tan, Z.; Sui, M.H.; Zhuang, Z.Q.; Liu, H.H.; Zheng, X.Y.; Yan, T.B.; Geng, D.F.; Jin, D.M. Nicotinic acetylcholine receptor $\alpha 7$ subunit mediates vagus nerve stimulation-induced neuroprotection in acute permanent cerebral ischemia by $\alpha 7$ nAChR/JAK2 pathway. *Med Sci. Monit.* **2017**, *23*, 6072–6081. [[CrossRef](#)]
580. Li, J.; Zhang, K.; Zhang, Q.; Zhou, X.; Wen, L.; Ma, J.; Niu, L.; Li, C. PPAR- γ Mediates Ta-VNS-Induced Angiogenesis and Subsequent Functional Recovery after Experimental Stroke in Rats. *BioMed Res. Int.* **2020**, *2020*, 8163789. [[CrossRef](#)]
581. Shields, R.W. Functional Anatomy of the Autonomic Nervous System. *J. Clin. Neurophysiol.* **1993**, *10*, 2–13. [[CrossRef](#)]
582. Pembroke, P. The anatomy of the vagus nerve in the cervical area in man. *J. Anat.* **1971**, *110*, 502. [[PubMed](#)]
583. George, M.S.; Aston-Jones, G. Noninvasive techniques for probing neurocircuitry and treating illness: Vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). *Neuropsychopharmacology* **2010**, *35*, 301–316. [[CrossRef](#)] [[PubMed](#)]
584. Stocker, S.D.; Sved, A.F.; Andresen, M.C. Missing pieces of the Piezo1/Piezo2 baroreceptor hypothesis: An autonomic perspective. *J. Neurophysiol.* **2019**, *122*, 1207–1212. [[CrossRef](#)] [[PubMed](#)]
585. Mueller, B.; Figueroa, A.; Robinson-Papp, J. Structural and functional connections between the autonomic nervous system, hypothalamic–pituitary–adrenal axis, and the immune system: A context and time dependent stress response network. *Neurol. Sci.* **2022**, *43*, 951–960. [[CrossRef](#)] [[PubMed](#)]
586. Berthoud, H.R.; Neuhuber, W.L. Functional and chemical anatomy of the afferent vagal system. *Auton. Neurosci. Basic Clin.* **2000**, *85*, 1–17. [[CrossRef](#)] [[PubMed](#)]
587. Jänig, W. Sympathetic nervous system and inflammation: A conceptual view. *Auton. Neurosci. Basic Clin.* **2014**, *182*, 4–14. [[CrossRef](#)]
588. Tracey, K.J. Reflex control of immunity. *Nat. Rev. Immunol.* **2009**, *9*, 418–428. [[CrossRef](#)]
589. Howland, R.H. Vagus Nerve Stimulation. *Curr. Behav. Neurosci. Rep.* **2014**, *1*, 64–73. [[CrossRef](#)]
590. Yuan, H.; Silberstein, S.D. Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review: Part III. *Headache: J. Head Face Pain* **2016**, *56*, 479–490. [[CrossRef](#)]
591. Mohanta, S.K.; Peng, L.; Li, Y.; Lu, S.; Sun, T.; Carnevale, L.; Perrotta, M.; Ma, Z.; Förster, B.; Stanic, K.; et al. Neuroimmune cardiovascular interfaces control atherosclerosis. *Nature* **2022**, *605*, 152–159. [[CrossRef](#)]
592. Ammons, W.S.; Blair, R.W.; Foreman, R.D. Vagal afferent inhibition of primate thoracic spinothalamic neurons. *J. Neurophysiol.* **1983**, *50*, 926–940. [[CrossRef](#)]
593. Randich, A.; Gebhart, G.F. Vagal afferent modulation of nociception. *Brain Res. Rev.* **1992**, *17*, 77–99. [[CrossRef](#)]
594. Hummel, T.; Sengupta, J.N.; Meller, S.T.; Gebhart, G.F. Responses of T2–4 spinal cord neurons to irritation of the lower airways in the rat. *Am. J. Physiol.-Regul. Integr. Comp. Physiol.* **1997**, *273*, R1147–R1157. [[CrossRef](#)]
595. Dorr, A.E.; Debonnel, G. Effect of Vagus Nerve Stimulation on Serotonergic and Noradrenergic Transmission. *J. Pharmacol. Exp. Ther.* **2006**, *318*, 890–898. [[CrossRef](#)]
596. Manta, S.; Dong, J.; Debonnel, G.; Blier, P. Enhancement of the function of rat serotonin and norepinephrine neurons by sustained vagus nerve stimulation. *J. Psychiatry Neurosci.* **2009**, *34*, 272–280.
597. Mesquita, R.N.O.; Taylor, J.L.; Trajano, G.S.; Škarabot, J.; Holobar, A.; Gonçalves, B.A.M.; Blazevich, A.J. Effects of reciprocal inhibition and whole-body relaxation on persistent inward currents estimated by two different methods. *J. Physiol.* **2022**, *600*, 2765–2787. [[CrossRef](#)]
598. Thorstensen, J.R. Persistent inward currents in spinal motoneurons: How can we study them in human participants? *J. Physiol.* **2022**. [[CrossRef](#)]
599. Burke, S.D.; Jordan, J.; Harrison, D.G.; Ananth Karumanchi, S. Solving baroreceptor mystery: Role of PIEZO ion channels. *J. Am. Soc. Nephrol.* **2019**, *30*, 911–913. [[CrossRef](#)]
600. Dampney, R.A.L.; Horiuchi, J.; Tagawa, T.; Fontes, M.A.P.; Potts, P.D.; Polson, J.W. Medullary and supramedullary mechanisms regulating sympathetic vasomotor tone. *Acta Physiol. Scand.* **2003**, *177*, 209–218. [[CrossRef](#)]
601. Moruzzi, G.; Magoun, H.W. Brain stem reticular formation and activation of the EEG. *Electroencephalogr. Clin. Neurophysiol.* **1949**, *1*, 455–473. [[CrossRef](#)]
602. Guyenet, P.G. The sympathetic control of blood pressure. *Nat. Rev. Neurosci.* **2006**, *7*, 335–346. [[CrossRef](#)]
603. Luccarini, P.; Gahery, Y.; Pompeiano, O. Cholinoceptive pontine reticular structures modify the postural adjustments during the limb movements induced by cortical stimulation. *Arch. Ital. De Biol.* **1990**, *128*, 19–45.
604. Quessy, S.; Freedman, E.G. Electrical stimulation of rhesus monkey nucleus reticularis gigantocellularis: I. Characteristics of evoked head movements. *Exp. Brain Res.* **2004**, *156*, 342–356. [[CrossRef](#)] [[PubMed](#)]

605. Schepens, B.; Drew, T. Descending signals from the pontomedullary reticular formation are bilateral, asymmetric, and gated during reaching movements in the cat. *J. Neurophysiol.* **2006**, *96*, 2229–2252. [[CrossRef](#)] [[PubMed](#)]
606. Takakusaki, K.; Chiba, R.; Nozu, T.; Okumura, T. Brainstem control of locomotion and muscle tone with special reference to the role of the mesopontine tegmentum and medullary reticulospinal systems. *J. Neural Transm.* **2016**, *123*, 695–729. [[CrossRef](#)] [[PubMed](#)]
607. Sparks, D.L.; Barton, E.J.; Gandhi, N.J.; Nelson, J. Studies of the role of the paramedian pontine reticular formation in the control of head-restrained and head-unrestrained gaze shifts. *Ann. N. Y. Acad. Sci.* **2002**, *956*, 85–98. [[CrossRef](#)]
608. Fung, S.J.; Chan, J.Y.H.; Manzoni, D.; White, S.R.; Lai, Y.Y.; Strahlendorf, H.K.; Zhuo, H.; Liu, R.H.; Reddy, V.K.; Barnes, C.D. Cotransmitter-mediated locus coeruleus action on motoneurons. *Brain Res. Bull.* **1994**, *35*, 423–432. [[CrossRef](#)]
609. Llorca-Torralba, M.; Borges, G.; Neto, F.; Mico, J.A.; Berrocoso, E. Noradrenergic Locus Coeruleus pathways in pain modulation. *Neuroscience* **2016**, *338*, 93–113. [[CrossRef](#)]
610. Pompeiano, O.; Horn, E.; D'Ascanio, P. *Locus Coeruleus and Dorsal Pontine Reticular Influences on the Gain of Vestibulospinal Reflexes*; Elsevier B.V.: Amsterdam, The Netherlands, 1991; Volume 88, pp. 435–462. [[CrossRef](#)]
611. van Neerven, J.; Pompeiano, O.; Collewyn, H. *Effects of GABAergic and Noradrenergic Injections into the Cerebellar Flocculus on Vestibulo-Ocular Reflexes in the Rabbit*; Elsevier B.V.: Amsterdam, The Netherlands, 1991; Volume 88, pp. 485–497. [[CrossRef](#)]
612. Pompeiano, O.; Manzoni, D.; D'Ascanio, P.; Andre, P. Noradrenergic agents in the cerebellar vermis affect adaptation of the vestibulospinal reflex gain. *Brain Res. Bull.* **1994**, *35*, 433–444. [[CrossRef](#)]
613. Sara, S.J. The locus coeruleus and noradrenergic modulation of cognition. *Nat. Rev. Neurosci.* **2009**, *10*, 211–223. [[CrossRef](#)]
614. Sara, S.J. Locus Coeruleus in time with the making of memories. *Curr. Opin. Neurobiol.* **2015**, *35*, 87–94. [[CrossRef](#)]
615. Sara, S.J.; Bouret, S. Orienting and Reorienting: The Locus Coeruleus Mediates Cognition through Arousal. *Neuron* **2012**, *76*, 130–141. [[CrossRef](#)]
616. Jurič, D.M.; Miklič, Š.; Čarman-Kržan, M. Monoaminergic neuronal activity up-regulates BDNF synthesis in cultured neonatal rat astrocytes. *Brain Res.* **2006**, *1108*, 54–62. [[CrossRef](#)]
617. Bekinschtein, P.; Cammarota, M.; Medina, J.H. BDNF and memory processing. *Neuropharmacology* **2014**, *76*, 677–683. [[CrossRef](#)]
618. McMorris, T. Developing the catecholamines hypothesis for the acute exercise-cognition interaction in humans: Lessons from animal studies. *Physiol. Behav.* **2016**, *165*, 291–299. [[CrossRef](#)]
619. Steriade, M.; McCormick, D.A.; Sejnowski, T.J. Thalamocortical oscillations in the sleeping and aroused brain. *Science* **1993**, *262*, 679–685. [[CrossRef](#)]
620. Steriade, M. Brain activation, then (1949) and now: Coherent fast rhythms in corticothalamic networks. *Arch. Ital. De Biol.* **1995**, *134*, 5–20.
621. Uhlhaas, P.J.; Pipa, G.; Lima, B.; Melloni, L.; Neuenschwander, S.; Nikolić, D.; Singer, W. Neural synchrony in cortical networks: History, concept and current status. *Front. Integr. Neurosci.* **2009**, *3*, 1–19. [[CrossRef](#)]
622. Hebb, D.O. *The Organization of Behavior: A Neuropsychological Theory*; Wiley: Oxford, UK, 1949; p. 335.
623. Löwel, S.; Singer, W. Selection of Intrinsic Horizontal Connections in the Visual Cortex by Correlated Neuronal Activity. *Science* **1992**, *255*, 209–212. [[CrossRef](#)]
624. Tyler, M.E.; Kaczmarek, K.A.; Rust, K.L.; Subbotin, A.M.; Skinner, K.L.; Danilov, Y.P. Non-invasive neuromodulation to improve gait in chronic multiple sclerosis: A randomized double blind controlled pilot trial. *J. Neuroeng. Rehabil.* **2014**, *11*, 1–10. [[CrossRef](#)]
625. Tramonti Fantozzi, M.P.; Artoni, F.; Di Galante, M.; Briscese, L.; De Cicco, V.; Bruschini, L.; D'Ascanio, P.; Manzoni, D.; Faraguna, U.; Carboncini, M.C. Effect of the Trigeminal Nerve Stimulation on Auditory Event-Related Potentials. *Cereb. Cortex Commun.* **2021**, *2*, 1–14. [[CrossRef](#)]
626. D'Arcy, R.C.N.; Greene, T.; Greene, D.; Frehlick, Z.; Fickling, S.D.; Campbell, N.; Etheridge, T.; Smith, C.; Bollinger, F.; Danilov, Y.; et al. Portable neuromodulation induces neuroplasticity to re-activate motor function recovery from brain injury: A high-density MEG case study. *J. Neuroeng. Rehabil.* **2020**, *17*, 1–12. [[CrossRef](#)] [[PubMed](#)]
627. Zheng, Y.; Mao, Y.R.; Yuan, T.F.; Xu, D.S.; Cheng, L.M. Multimodal treatment for spinal cord injury: A sword of neuroregeneration upon neuromodulation. *Neural Regen. Res.* **2020**, *15*, 1437–1450. [[CrossRef](#)] [[PubMed](#)]
628. Makin, T.R.; Scholz, J.; Filippini, N.; Henderson Slater, D.; Tracey, I.; Johansen-Berg, H. Phantom pain is associated with preserved structure and function in the former hand area. *Nat. Commun.* **2013**, *4*. [[CrossRef](#)] [[PubMed](#)]
629. Simões, E.L.; Bramati, I.; Rodrigues, E.; Franzoi, A.; Moll, J.; Lent, R.; Tovar-Moll, F. Functional expansion of sensorimotor representation and structural reorganization of callosal connections in lower limb amputees. *J. Neurosci.* **2012**, *32*, 3211–3220. [[CrossRef](#)] [[PubMed](#)]
630. Ehrsson, H.H.; Rosén, B.; Stockselius, A.; Ragnö, C.; Köhler, P.; Lundborg, G. Upper limb amputees can be induced to experience a rubber hand as their own. *Brain* **2008**, *131*, 3443–3452. [[CrossRef](#)]
631. Shokur, S.; O'Doherty, J.E.; Winans, J.A.; Bleuler, H.; Lebedev, M.A.; Nicolelis, M.A.L. Expanding the primate body schema in sensorimotor cortex by virtual touches of an avatar. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 15121–15126. [[CrossRef](#)]

-
632. Beech, D.J. Endothelial Piezo1 channels as sensors of exercise. *J. Physiol.* **2018**, *596*, 979–984. [[CrossRef](#)]
633. Ghazi, M.; Rippetoe, J.; Chandrashekhar, R.; Wang, H. Focal vibration therapy: Vibration parameters of effective wearable devices. *Appl. Sci.* **2021**, *11*, 2969. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.