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Review

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

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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

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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].

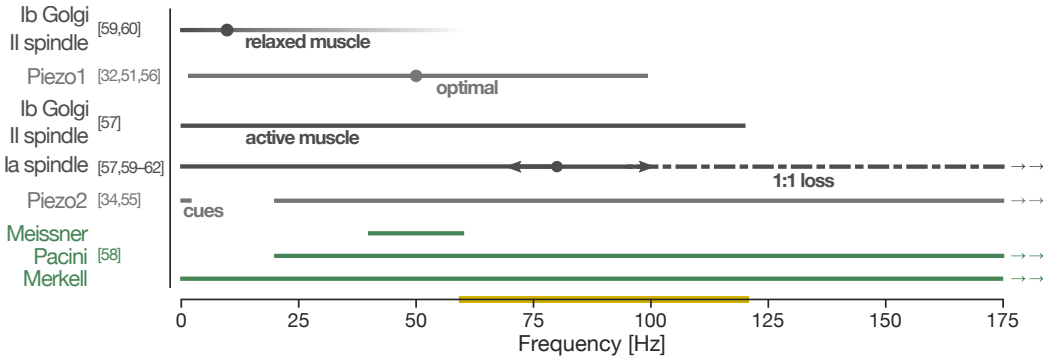

Figure 1. Frequency encoding of mechanically sensitive receptors. Colors: recommended range for focal muscle and tendon vibration and vibrotactile feedback—dark yellow on axis; touch—green [58], proprioception—black [57,59–62], and Piezos—gray [32,34,51,55,56].

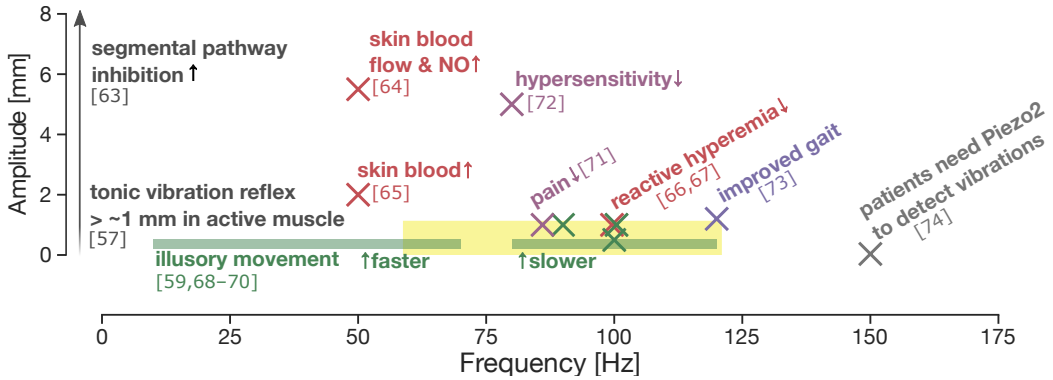

Figure 2. Physiological responses to focal vibration amplitude and frequency. Illusory movement speed induced by increasing tendon vibration frequency is either perceived as becoming faster at frequencies < 70 Hz or as slower at >80 Hz [59]. Note that the tonic vibration reflex occurs independently of 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 Aδ 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 µm amplitude (Figure 2, correct detection of patients vs. control; mean ± standard deviation: 40 ± 14% vs. 98 ± 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 ± 10% vs. 100%, respectively) [74]. Similar to healthy participants, these two patients detected non-noxious deep tissue pressure already at 30 mmHg, whereas Aβ-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 °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) Aβ fibers (Aβ SA-LTMRs); fast-conducting, thickly myelinated, rapidly adapting (RA) Aβ fibers (Aβ RA-LTMRs); medium-conducting (~5–30 m/s), thinly myelinated Aδ fibers (Aδ 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 Aβ and Aδ 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 Aβ, Aδ, 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 mm^2), the Pacinian corpuscle with RA2 (39–5223 mm^2), the Merkel cell–neurite complex with SA1 (5–29.5 mm^2), and the dermal Ruffini corpuscles with SA2 (7–1346 mm^2) [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 Aβ LTMRs [2,31,58,74,127,128,132,195] and Aδ 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 (Aβ 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 (Aβ 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].

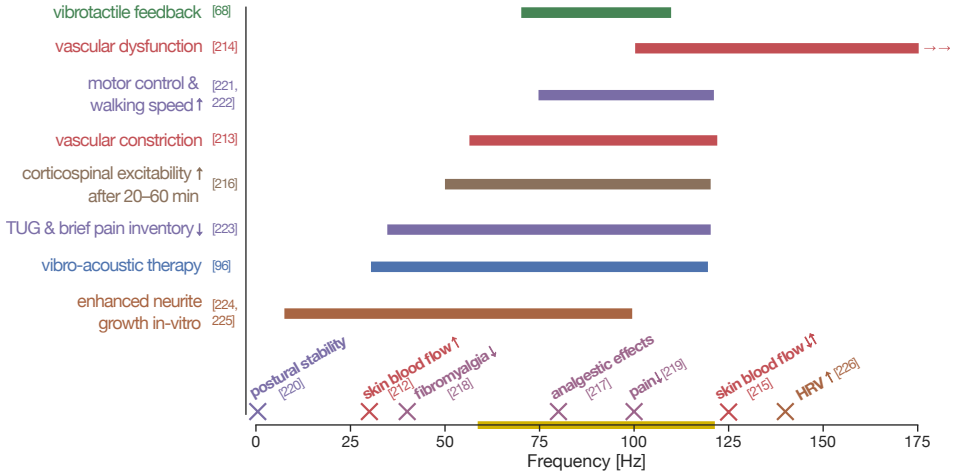

Figure 3. Physiological response to various focal vibration frequencies. Colors: recommended range for focal muscle and tendon vibration and vibrotactile feedback—dark yellow on axis; studies on the vascular system are marked in red [212–215]; sensory feedback and touch—green [68]; corticospinal excitability—brown [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 (Aβ 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 (Aβ SA2-LTMR) lie in the reticular layer of the dermis and within joints [227]. In the human skin, their density is <0.3 corpuscles/mm^2, where they sense stretching of the skin around objects and over joints [208,209]. While neurophysiological recordings identified neurons with properties corresponding to Aβ SA2-LTMR [228], morphological analysis often did not find Ruffini corpuscles within the expected regions of the skin [229]. Thus, the association between Aβ 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 Aβ fibers exclusively signal aspects of touch, Aδ and C fibers signal pain in addition to temperature and gentle touch (Figure 4) [138,230–234].

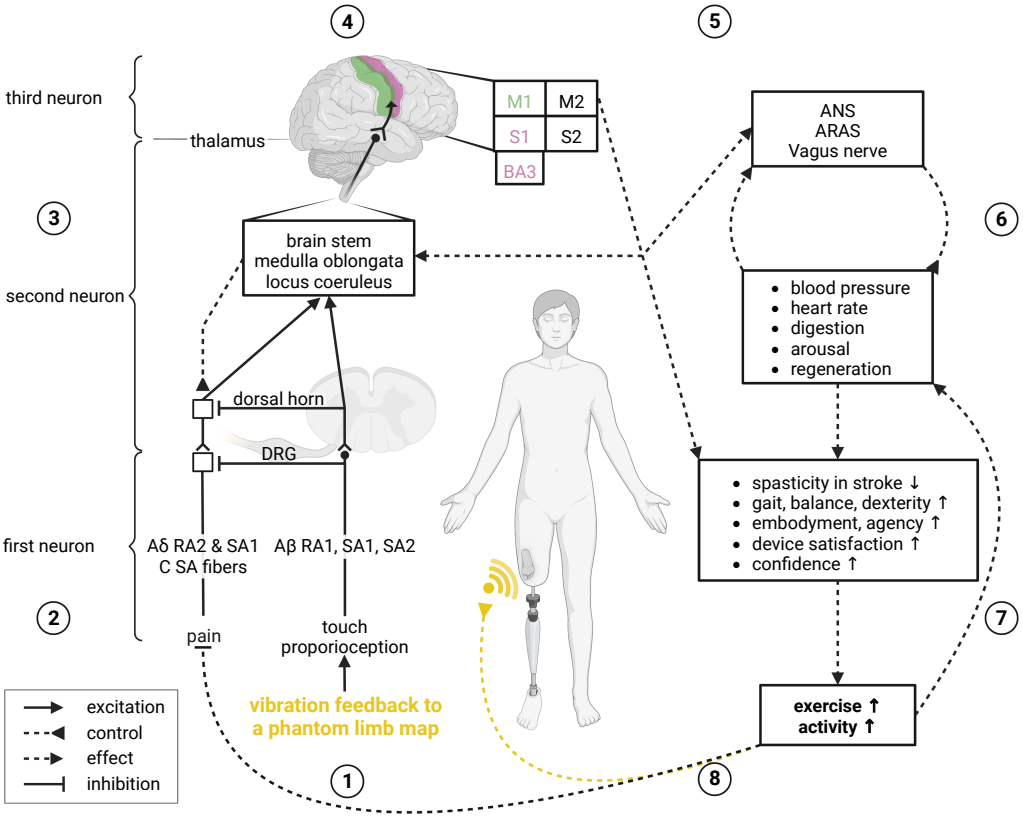

Figure 4. General neuromodulation pathways of vibratory feedback. (1) Focal vibration stimulates an area that a person associates with a denervated limb [235]; (2) afferent signals of touch and proprioception travel through first-order neurons to the DRG [14], where they can inhibit pain already

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 α2-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 ~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±SD for frequency is 94 ± 16 Hz, and for amplitude, it is 0.5 ± 0.4 mm (Figure 5).

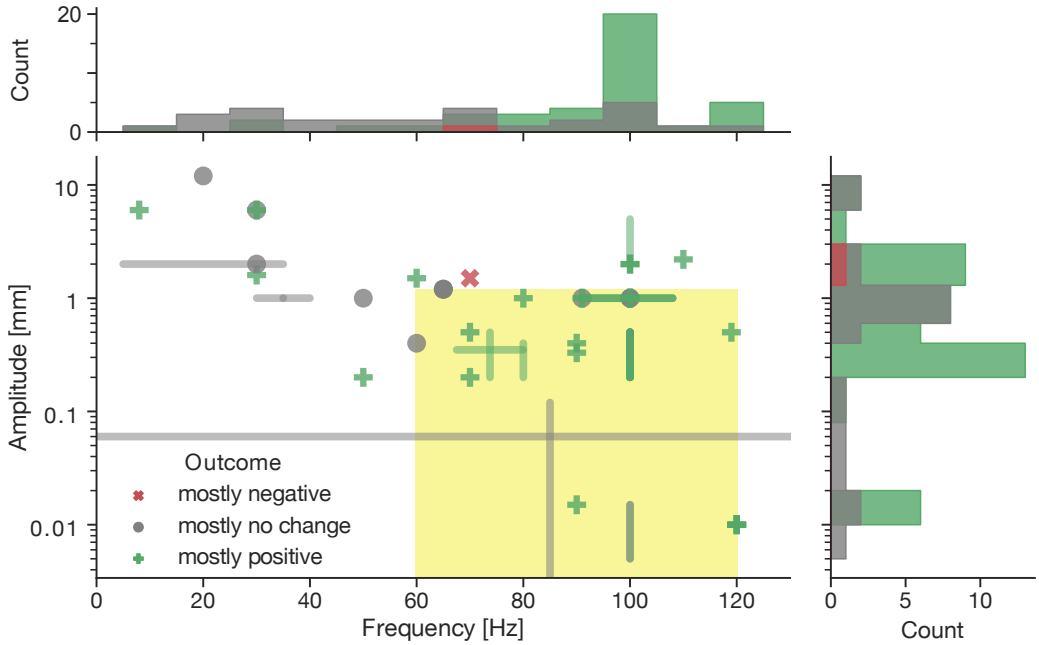

Figure 5. Color-coded scatter plot and histograms of frequencies and amplitudes used in 61 intervention groups from 56 studies on focal muscle or tendon vibration [216,266,267,277–280,282–298,301–324,326–329] that were selected by nine recent systematic reviews [268–276]. Parameter ranges from studies 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 adaptions. 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].

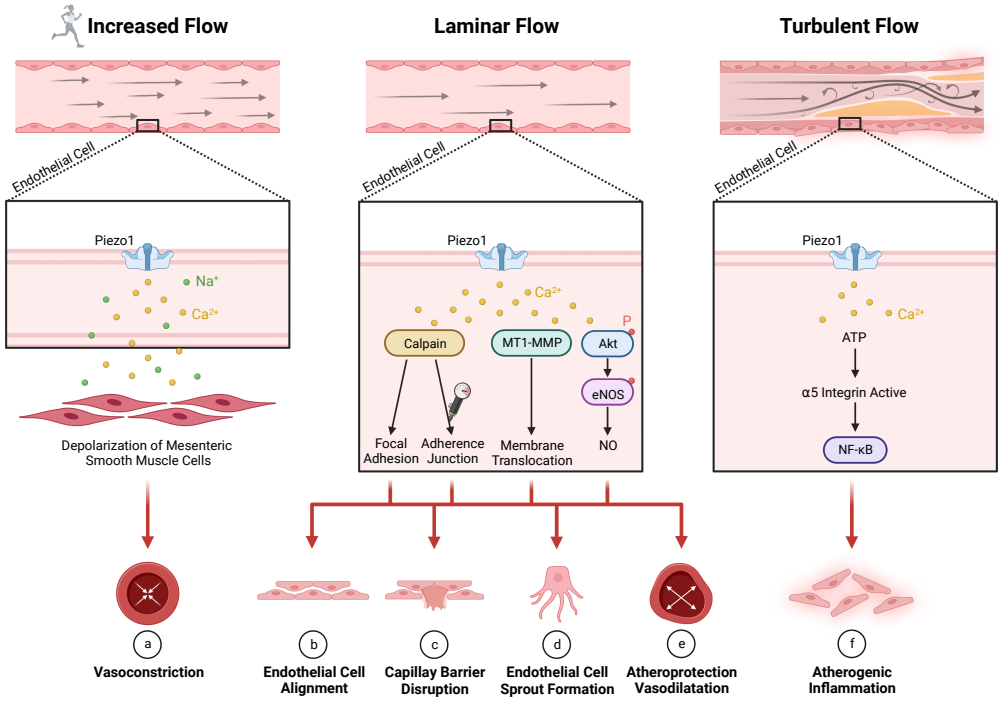

Figure 6. The signaling pathways and outcomes of Piezo1 activation in the endothelium depend on blood flow direction, frequency, and intensity [34,35,40,86,107,367–369].

(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) NF-κB [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 ribo-

somes 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 neurothropic 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 neurothropic 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 imporant 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-κB 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 adaptions.

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. Embodyment 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, muscular 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 brainstem, 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 α2-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.

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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	Brodmann 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

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