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Opinion

Does Proprioception Involve Synchronization with Theta Rhythms by a Novel Piezo2 Initiated Ultrafast VGLUT2 Signaling?

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Abstract: This opinion manuscript outlines how the hippocampal theta rhythm could receive two novel peripheral inputs. One of the ways this could be achieved is through Piezo2 channels and atypical hippocampal-like metabotropic glutamate receptors coupled to phospholipase D containing proprioceptive primary afferent terminals. Accordingly, activated proprioceptive terminal Piezo2 on Type Ia fibers synchronizes to the theta rhythm with the help of hippocampal Piezo2 and medial septal glutamatergic neurons. Second, after baroreceptor Piezo2 is entrained to activated proprioceptive Piezo2, it could turn on the $Ca_v1.3$ channels, which pace the heart rhythm and regulate pacemaker cells during cardiac sympathetic activation. This would allow the $Ca_v1.3$ channels to synchronize to theta rhythm pacemaker hippocampal parvalbumin-expressing GABAergic neurons. This novel Piezo2-initiated proton–proton frequency coupling through VGLUT2 may provide the ultrafast long-range signaling pathway for the proposed Piezo2 synchronization of the low-frequency glutamatergic cell surface membrane oscillations in order to provide peripheral spatial and speed inputs to the space and speed coding of the hippocampal theta rhythm, supporting locomotion, learning and memory. Moreover, it provides an ultrafast signaling for postural and orthostatic control. Finally, suggestions are made as to how Piezo2 channelopathy could impair this ultrafast communication in many conditions and diseases with not entirely known etiology, leading to impaired proprioception and/or autonomic disbalance.

Keywords: hippocampal theta rhythm; Piezo2 channel; VGLUT2; $Ca_v1.3$ channel; PLD-mGluR; Piezo2 channelopathy

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1. Introduction

Theta rhythms (TR) are generated by neural oscillation-based based theta waves (ranging from 4 to 12 Hz) in the hippocampus, which are involved in learning, memory, spatial navigation, locomotion, attention and arousal [1]. The hippocampus is a critical brain locus where sensory information is processed in terms of navigation, learning and memory consolidation [2], but its role in stress regulation should not be overlooked [3]. It has long been known that the electrical stimulation of the hippocampal formation correlates with the intensity of physical activity by constructing an exercise–brain axis [1]. However, it is not entirely known how these neurological changes are generated in the hippocampus, e.g., whether they are generated from the hippocampus itself or from another source of peripheral inputs, such as from muscle-derived circulating factors [1]. An especially intriguing question is how the hippocampal formation abruptly correlates with the onset and duration of voluntary strenuous physical exercise represented in the TR in addition to the question of how this is proportionally speed dependent [4].

The low-frequency (LF) power of heart rate variability (HRV) also shows a correlation, albeit a negative one, with voluntary medium to high-intensity exercise at the onset, and this mechanism is theorized to be largely attributed to the activity level of Piezo2 ion

channels in the baroreceptors [5]. Furthermore, these Piezo2 ion channels are shown to be the principal mechanotransductory ion channels responsible for proprioception [6]. Proprioception is a mysterious, diagnostically challenging system referring to the sense of the positions and actions of the extremities. The functional role of Piezo2 in muscle spindle-derived proprioceptive primary sensory afferent terminals is highlighted through a mechanism theory of delayed onset muscle soreness (DOMS) [7]. It is important to note that the role of these intrafusal proprioceptive afferents in learning and memory has also been emphasized [8]. Hence, these proprioceptive functions show a time overlap on the periphery with the central functionality of TRs, especially pertaining to the aforementioned exercise, learning, memory and spatial navigation dimensions.

When voluntary unaccustomed and/or strenuous exercise is performed, the microinjury of these proprioceptive terminal Piezo2 ion channels is considered to be the primary damage phase. This could lead to DOMS in the presence of the secondary injury phase [9]. This proposed Piezo2 channelopathy equivalent primary damage is implicated in other conditions and diseases as a consequence of autogenic microinjury of Piezo2 in sensory terminals contributing to proprioception. Hence, it evolves in DOMS [7,9], in addition to evolving in dry eye disease (DED) [10], psoriasis [11], osteoporosis [12], and amyotrophic lateral sclerosis (ALS) [13–15], and it is suspected in even more conditions [16]. Interestingly, all of these conditions and diseases come with impaired proprioception and autonomic disbalance or dysregulation in addition to their association with dysregulated TRs or cognitive impairments.

Piezo2 ion channels could provide neural intrinsic resonance-based synchronization between neural networks within the brain [17]. This paper provides context for the possibility that Piezo2 ion channels could initiate synchronization with TR when middle- and high-intensity voluntary exercise activity begins. Presuming that Piezo2 provides the neural intrinsic resonance in baroreceptors and intrafusal proprioceptive terminals, these terminals could synchronize with hippocampal Piezo2 as peripheral inputs from the turn-ON phase of TR activation when middle- and high-intensity exercise activity is initiated or even prior to it in the voluntary preparatory phase. This abruptly activated intrinsic Piezo2-based resonance derived ultrafast signaling could be a novel synchronizing communication that is a lot faster than neurotransmitter-based or peripheral muscle-derived circulating factor-based ones within the nervous system. The Piezo2 channelopathy-induced calcium homeostasis dysregulation in this impaired novel resonance-based cross-frequency coupled communication is proposed to be a principle gateway to pathophysiology. This could provide significant insight into the onset and chronification of the aforementioned conditions and diseases with not entirely known etiology, e.g., mild traumatic brain injury (mTBI). Exercise, sleep and other conditions and diseases, like DOMS, diabetes, mTBI and ALS, will be used as examples in support of this novel Piezo2-based theoretical signaling mechanism, which might have a principal gatekeeping role in whole-body homeostasis regulation.

2. Piezo2 Channel and Its Channelopathy

Piezo ion channels are evolutionarily conserved, mechanotransductory ion channels and are non-selective, although they do demonstrate a preference for calcium [18,19]. In humans, two forms of Piezo ion channels are present: Piezo1 and Piezo2. These proteins are the largest transmembrane proteins known so far with the capabilities of inducing kinetically differentiated mechanically activated currents [19]. Piezo2 participates in the detection of indentation, compression, stretch, fine touch, shear stress or vibration, but it is also involved in the regulation of cell homeostasis. Even more important again, Piezo2 was identified as the principal mechanotransduction channel for proprioception [6]. Our knowledge of their features, functionality and gating characteristics are emerging rapidly, but our knowledge is short from complete. In relation to the elevated focus on this research trend, Ardem Patapoutian received the Nobel Prize lately for identifying Piezo ion channels. Nonetheless, one important feature of Piezo2 is its instantaneous activation that initiates electrical signaling in proprioceptive primary sensory afferents. This abrupt activation

provides maintained and amplified consistent firing by $Na_v1.1$ channels upstream [20]. Hence, when muscle stretch is prolonged and Piezo2 is inactivated, $Na_v1.1$ is still needed for adequate and sustained firing and proprioceptive signaling [20].

2.1. Potential Relevance of Membrane Compartments and Oscillation

It was hypothesized that muscle spindle derived proprioceptive sensory afferent terminal Piezo2 could go through an autogenic microdamage under an acute stress response (ASR) time window [9]. Part of this Piezo2 channelopathy theory is that these channels should be viewed as homeostatic gatekeepers of peripheral sensory neurons in a compartmental micromilieu. On the contrary, Piezo1 ion channels are the homeostatic gatekeepers of the surrounding peripheral cells within these affected compartments [10]. Compartmentalization is known to be an important underlying structure in the central nervous system. As an analogy, the current author emphasizes the relevance of compartments in the periphery as a conserved ontogenetic developmental pattern. In support, the acute compression axonopathy theory of DOMS highlights that muscle spindles have selective barriers, like the blood–brain barrier (BBB) or blood–spinal cord barrier (BSCB) [21]. Hence, Piezo2 not only could have a role in intracranial pressure pulse transduction [17] but might transduce pressure pulse from peripheral compartments as well. Furthermore, Piezo channels are tethered to the intracellular actin cytoskeleton, and the perturbation of this tethering is also detected by these channels [22]. It is important to note that proprioceptive sensory afferents are pseudo-unipolar neurons. Thus, they are riding through selective barriers from the periphery into the central nervous system (CNS) by crossing the BSCB. This feature of these neurons lets them transduce the aforementioned Piezo2-derived neural intrinsic resonance-based signaling from the periphery to the CNS. Moreover, this Piezo2 resonance could be coupled with Piezo1 containing peripheral cell resonance in the absence of Piezo2 channelopathy. Accordingly, it Is suggested that Piezo2 channelopathy impairs the crosstalk between somatosensory terminal Piezo2 and Piezo1 of the surrounding peripheral cells within the affected peripheral compartmental micromilieu [10].

2.2. Potentially Critical Role of Syndecans in the Piezo2–Piezo1 Crosstalk

The crosstalk between Piezo2 and Piezo1 has been implicated both in synergistic and negative interaction, depending on Piezo1-containing cell types [10,23–25]. Syndecan is suggested to be a critical medium in this Piezo2–Piezo1 crosstalk [16]. Syndecans are transmembrane proteoglycans with four family members, and syndecane-3 is the largest amongst them. Every cell contains syndecans with unique cell, tissue and developmental representation, and they may have redundant characteristics; hence, they could compensate for each other [26]. Syndecan-3 is abundantly represented in the CNS in a distinct manner, but their localization and functional role on the periphery is also emerging [27]. Syndecane-3 has a central role in certain neurons, like in cell adhesion, migration and neurite outgrowth, in an actin-dependent manner [28]. Hence, their transmembrane localization serves as an important link between the actin cytoskeleton and the extracellular matrix (ECM). Even more importantly, hippocampal syndecane-3 also participates in spatial memory encoding [29]. The nerve injury of primary afferent neurons is known to induce syndecan-1 expression in dorsal root ganglions (DRGs) [30], but the current author suspects it as a redundant compensatory mechanism due to the functional loss of the syndecan-3 containing injured primary afferents or autogenic syndecane-3 depletion on these proprioceptive terminals, as is suggested in DOMS. It is noteworthy that syndecan-1 and syndecan-3 are important paralogs of each other, but they are not homologs. Part of the Piezo2 channelopathy theory is that glutamate vesicular release is also impaired [9], and it is known that syndecans may have a governing role in vesicular trafficking [31]. It is interesting to note that the aforementioned atypical glutamate receptor containing primary afferents indeed controls stretch sensitivity [32]. Enhanced mechanotransduction is suggested to induce syndecan clustering and shedding on the extracellular domain in unconventional cholesterol rafts, as syndecans also control vesicular trafficking pathways [31].

However, the excessively prolonged mechanostransduction, leading to the suggested transient Piezo2 microinjury, is proposed to deplete membrane cholesterol around Piezo2 [7]. Therefore, this shortage of localized membrane cholesterol and resultant syndecan clustering inhibition may explain the lost control of vesicular trafficking, leading to impaired glutamate vesicular release and eventually to glutamate excitotoxicity [8,13].

2.3. Piezo Ion Channels as Shottky Diods, Extracellular Surface Syndecans as Antennas and ECM as a Semiconductor

That being so, the author of this manuscript suggests that intrafusal syndecans-3, in cahoots with extrafusal snydecan-1, could act like an ECM semiconductor antenna with localized surface plasmon resonance, when electrons oscillate collectively, in the peripheral Piezo crosstalk [33]. It is noteworthy that the acute compression axonopathy theory of DOMS suggested that the mitochondrial electron transport chain generated free radical production as a factor leading to the primary injury phase of DOMS [21]. This primary microdamage was later called Piezo2 channelopathy [7]. In support, the lost function of Piezo2 indeed impairs nitric oxide synthases and stimulates remodeling [34] as was theorized by the acute compression axonopathy theory of DOMS [21] and later by the Piezo2 channelopathy theory [7].

In summary, this collective electron-based resonance mechanism may underpin the suspected Piezo crosstalk. In addition, this theoretical mechanism may support the later mentioned ultrafast signaling where the activated Piezo2 could be synchronized with the turn-ON signal of TR. Moreover, the aforementioned feature of syndecans will result in resonant absorption, scattering and near-field enhancement depending on the membrane localization of syndecans. Hence, when syndecans translocate to the nucleus of cells [35], then there is a reverse bias conduction role with minimal forward current between the Piezo2–Piezo1 crosstalk. In contrast, when syndecans are on the extracellular surface, then they behave like a semiconductor antenna in order to facilitate forward bias within the nano-semiconductor-like ECM, leading to a substantial forward current in Piezo2–Piezo1 crosstalk. Therefore, syndecans could provide a reverse bias condition in the current conduction, as well as reverse osmosis, resulting in reverse homeostatic mechanotransduction within the compartmental micromilieu. In this model, Piezo2 may behave like a low-frequency Shottky barrier semiconductor diode, meaning that when the noise level decreases abruptly, then the ideality factor tends to unify. In contrast, when the noise level increases very fast, then it follows a reverse course. Indeed, Piezo channels have these fast activating characteristics [20] in addition to their aforementioned capability of providing intrinsic resonance to certain neurons [17]. Excessively prolonged mechanotransduction on syndecans could induce shedding which will promote cell migration and could alter its negative charge on the cellular surface; hence, it could alter and eventually impair the Piezo crosstalk in the compartmental micromilieu [16]. Consequently, adequate syndecan supply and unimpaired extracellular representation seems to be needed in proprioceptive excitation not to mention their role in regeneration. In support, the redundant features of proteoglycans and syndecans could be the reason why the administration of synthetic proteoglycans may reverse neuron regeneration disruption [36].

2.4. Piezo2 Channelopathy as Inflammatory/Gateway Reflex Inducer

The Piezo2 channelopathy-derived impaired Piezo2–Piezo1 crosstalk [16] could be one initiator of the so-called neural circuit-based inflammatory reflex [37]. Correspondingly, the impaired Piezo2–Piezo1 crosstalk-induced lost control of Piezo1 may provide a transient permeability increase on the selective barriers and vasculature based on the work of Zhang et al. and Fletcher et al. [38**?**]. It is indicative that Piezo2 channelopathy on Type Ia proprioceptive terminals may limit static phase firing encoding only to Type II fibers [40], and only these intrafusal Type II proprioceptive fibers express Tac1 genes with a likely role in inflammatory muscle pain [41].

Another consequence of this impaired crosstalk is the activation of dendritic cells with upstream Piezo1 downregulation and the activation of keratinocytes (likely myocytes as well) with upstream Piezo1 upregulation [11,36]. Piezo2 channelopathy also activates the first-line innate immune system protection by natural killer (NK) and NKT cells with an imbalanced control of NKT cell response [42]. It is noteworthy that the involvement of syndecans in the activation of the NKT cell subpopulation is implicated [16]. It is hypothesized that under excessively prolonged mechanotransduction within an ASR time window, the self-eating of mitochondrial and intracellular debris is incomplete as a consequence of the "leaky" neuron terminals due to the microdamage of Piezo2. Thus, this debris could activate the first-line innate immune response [11]. It should be also noted that mitochondria are derived from bacteria evolutionarily [11] and proprioceptive terminals are suggested to have high mitochondria content, especially under proprioceptive loading [21]. Moreover, the proposed neuron terminal debris is likely not familiar to the immune system of the host due to the immune privileged status of the CNS. Hence, it could even lead to autoimmune diseases when underlying genetic disposition is present [11,16].

This Piezo2 channelopathy-induced impaired Piezo2–Piezo1 crosstalk is also framed as the aforementioned potential gateway between physiology and pathophysiology [10]. In addition, the Piezo2 channelopathy-derived impaired Piezo2–Piezo1 crosstalk in the affected peripheral compartmental micromilieu and the transiently increased permeability of its selective barrier could result in the dysregulation of the intracompartmental pressure pulse mechanotransduction. This impaired mechanotransduction is in addition to the invasion of immune cells due to the inducement of neural circuit-based inflammatory reflex [16]. The chronification of this reflex pathway inducement could be equivalent to the gateway reflex [16].

2.5. Intracellular Mitochondria Oscillation

It is important to note that Piezo2 channelopathy theory also implied the energy-depleted dysfunctionality of mitochondria in the overloaded intrafusal proprioceptive terminals during this mechano-energetic microdamage [9]. Aon et al. suggested that high-frequency (HF) oscillations could be induced by reactive oxygen species (ROS) production in mitochondria [43]. Hence, an ROS-dependent mitochondrial oscillator-based signaling transduction pathway may exist in cardiomyocytes and myocytes. This signaling is frequency and amplitude-modulated with the capability of regulating even gene transcription [43]. Correspondingly, proprioceptive Piezo2 channelopathy is theorized to be one principal transcription activator [14]. The current author suspects an analogue mitochondrial HF oscillation induced signaling transduction in intrafusal myocytes and intrafusal proprioceptive terminals under prolonged proprioceptive excitation leading to allostasis. Huygens synchronization, meaning a mechanism that oscillators at different frequencies could synchronize at higher excitation within their frequency domain, and pathological conditions could couple these mitochondrial oscillations at HF within the mitochondrial network of the cardiomyocytes [44]. Accordingly, prolonged and excessive proprioceptive mechanotransduction could induce the synchronization of mitochondrial oscillations at HF in intrafusal myocytes and proprioceptive terminals.

Another important feature of this transduction pathway could be that mitochondria are organized in a precisely ordered "crystal-like" pattern. Moreover, they could also undergo a rapid transition when the pattern becomes a radically symmetric one [45]. This transitional mitochondrial pattern generation could be especially interesting in neurons. Axonal mitochondrial trafficking carries high importance in order to supply mitochondria by microtubules or actin filaments to high-energy-demanding sites [45]. The proprioceptive loading-derived enhanced trafficking of mitochondria to proprioceptive terminals is theorized under repetitive eccentric contractions [21]. The current author proposes that mechanotransductory Piezo1 ion channels convert the mitochondrial HF oscillator-based signaling from cardiomyocytes and myocytes under a "crystal-like" pattern to an LF signal. This LF signal is transduced further by syndecan-1 antennas and ECM nano-semiconductors

on the periphery toward syndecan-3 and proprioceptive Piezo2. Conversely, Piezo2 ion channels convert mitochondrial HF oscillator-based signaling in proprioceptive terminals under a "crystal-like" pattern to an LF signal. This proprioceptive LF signal is transduced further between syndecans-3 and syndecan-1 antennas of Piezo1 containing peripheral cells. ECM functions again as a nano-semiconductor in this reverse Piezo crosstalk.

However, when the energy supply is in high demand, the "crystal-like" pattern could go under transition toward a radically symmetric one. This is when the Piezo2 ion channels could be inactivated at the proprioceptive terminals. Accordingly, the "crystal-like" pattern of mitochondria, like in the case of crystals, could have relevance in HF oscillation conduction as crystal-like structures of ECM proteins under LF oscillation transduction [46]. Nevertheless, even the radically symmetric pattern of mitochondria may not provide a sufficient supply of energy when the mitochondrial energy supply is perturbed under unaccustomed or strenuous eccentric exercise-derived allostasis. Hence, this excessively prolonged proprioceptive mechanotransduction may explain the energy-depleted dysfunctionality of mitochondria underpinning Piezo2 channelopathy.

2.6. Mild Traumatic Brain Injury

It is noteworthy that Piezo2 is also detected in the CNS, namely in the neocortex and in pyramidal cells of the hippocampus. Even more importantly, the expression of these channels is increased due to repetitive mechanical injuries, like blast TBI [47]. Furthermore, concussion and mTBI could cause the abrupt overactivation of Piezo2 channels in association with likely reversible brain functional disruption, loss of memory and consciousness [17]. However, the current author emphasizes that the overstretching of the neck muscles and their intrafusal Piezo2 ion channels in these TBI injuries are not factored into the injury mechanism. Correspondingly, it may not be enough to consider the intracranial compartmental micromilieu only. These neck muscle spindles are behaving like "breaks" [48]; hence. the author of this paper suggests that sudden overstretching-induced peripheral proprioceptive terminal Piezo2 channelopathy will add to the complexity of the mTBI/blast TBI injury mechanism. The lost proprioceptive protection of neck muscle spindles may result in an abrupt whiplash phenomenon, leading to enhanced intracranial neural microdamage. Accordingly, the increased expression of Piezo2 in brain neurons of TBI could be the compensatory consequence of intracranial Piezo2 channelopathy induced by the aforementioned impaired functionality of Piezo2 in neck muscle spindles. This may also mean that the gating through these channels is impaired [9]; hence, they could not sufficiently sense the homeostatic intracranial pressure load in the affected compartmental micromilieu.

3. Theta Rhythm Onset and Synchronization

The precise identification of the pacemaker of TR has been an open question for a long time regardless of whether the septum-diagonal band of Broca inactivation ceases theta waves [4]. A recent study verified the earlier explored [49] parvalbumin (PV)-expressing GABAergic neurons as pacemakers of TR. In addition, the medial septal (MS) glutamatergic neurons were identified as tonic theta ON type [50]. Correspondingly, these MS glutamatergic neurons increase the excitation during the hippocampal theta state from the onset but do not follow TR; rather, there is a tonic drive to pacemakers in order to induce theta [50]. Furthermore, this study also confirmed that MS pacemaker neurons follow Huygens synchronization [50]. Accordingly, MS VGLUT2 expressing glutamatergic neurons at 20 Hz frequency, which is higher than theta range, were capable of inducing theta oscillation, and these results could substantiate how these types of neurons could induce TR turn-ON in a locomotion-dependent manner [50]. Indeed, hippocampal TR is ON instantaneously from the beginning and as long as strenuous voluntary physical activity maintained [1,4]. Moreover, this hippocampal rhythmic synchronous firing is increased in correlation with speed [1].

3.1. Peripheral Tonic Drive as Input to Theta Rhythm

Another interesting recent finding is that tonic drive could be evoked by atypical hippocampal-like metabotropic glutamate receptors coupled to phospholipase D (PLD-mGluR) on intrafusal proprioceptive primary afferent terminals [32]. This study not only confirms earlier suspected mGluR at these proprioceptive terminals [20] but could raise further importance to Piezo2 contents in these nerve endings. As mentioned before, Piezo2 has the characteristics of abrupt activation and inactivation at prolonged stretches [20]. Hence, the current author suggests that the contribution of these features of Piezo2 channels is needed on intrafusal glutamatergic neurons in order to synchronize to the turn-ON phase of TR. In support, Piezo2 channels are indeed also present at the hippocampus [17].

Moreover, it was theorized that the LF power of HRV represents the activation level of Piezo2 in the baroreceptors [5]. It is noteworthy again that the LF power also follows a similar correlation with the onset of physical activity, like TR; however, it is a negative one. The activation of Piezo2 may initiate the synchronization of the aforementioned correlation with TR during physical activity. Based on this hypothesis, it is reasonable to suspect that when TR is initiated or turned-ON with the assistance of MS glutamatergic neurons, then it is a window of opportunity for synchronization by activated Piezo2 on PLD-mGluR containing proprioceptive primary afferents and in baroreceptors coupling with activated hippocampal Piezo2. It has been considered that locomotion, running speed, and spatial location are all linked to TR [3], and the current novel proprioceptive Piezo2-based synchronization into the turn-ON of TR would provide the peripheral input to these central hippocampal links. The coding of space and time dimensions of TR by these inputs are pivotal to serve episodic memory [51]; however, the exact mechanism of how TR serves memory function is not known [3].

The recent molecular and optogenetic tracing of proprioceptive primary afferents may highlight the basis for the above proposed synchronization mechanism. It was shown that input from PV-expressing proprioceptive afferents could tonically suppress nociceptor activation in the DRG [52]. The current author suggests that this finding uncovers the mechanism behind exercise-induced analgesia as was theorized in the acute compression axonopathy theory of DOMS [21]. In addition, these PV-expressing proprioceptive sensory neurons are suggested to be analogous with the PLD-mGluR-containing ones. It is important to highlight that another study rightly distinguishes between the static and dynamic sensitivity of Type Ia and Type II proprioceptive afferents [41]. Correspondingly, Type II proprioceptive afferents barely represent dynamic sensitivity, while Type Ia proprioceptive fibers convey both static and dynamic encoding [41]. Hence, the prolonged stretch could enhance the glutamatergic activation of PLD-mGluR containing Type Ia afferents, providing the tonic suppression of nociception if present. However, these tonic glutamatergic Type Ia terminals could be microinjured by certain chemotherapy and DOMS-inducing exercise [8], leading to significantly delayed medium-latency response [40] and an unimpaired short-latency response of the stretch reflex [40,53]. It is important to note that this Type Ia terminal microinjury is suggested to be the Piezo2 channelopathy [9,13,40], leading to miswired proprioception [14]. Interpreting the findings of Fuller et al. [52], the activation of Type II proprioceptive afferents by DOMS-inducing exercise would tonically suppress nociception in the dorsal root ganglion by GABA release from the somata of these neurons temporarily. This proprioceptive repression of nociception is the equivalent of exercise-induced analgesia; however, this would not stop the Piezo2 channelopathy-derived imbalanced leakage Ca^{2+} subthreshold currents and glutamate on activated PLD-mGluR-containing glutamatergic Type Ia afferents. Even more precisely, the proposed impaired glutamate vesicular release associated with Piezo2 channelopathy in DOMS could lead to a higher activation of glutamate decarboxylase and hence higher GABA generation from glutamate in the DRG. The higher level of GABA uptake transporter on Type Ia afferents [52] may serve this purpose.

3.2. Protons as Neurotransmitters in a Novel Ultrafast Signaling

The unusual presence of VGLUT2 on Type II afferents [52] could be explained by the buffering of Piezo2 inactivation on Type Ia fibers and the buffering of acute Piezo2 channelopathy-induced temporary proprioceptive miswiring and VGLUT1 synaptic disconnection [14]. Thus, not only MS glutamatergic neurons are expressing VGLUT2 [50] but the DRG of muscle spindle-derived proprioceptive afferents as well [52]. The VGLUT2 content on primary glutamatergic neurons and secondary Type II afferents may support locomotion by static phase firing encoding. In support, locomotion is indeed initiated and controlled by MS VGLUT2 glutamatergic neural circuits not to mention that these neurons also couple TR and CA1 activity in a speed-dependent manner [54]. It is indicative as well that the elimination of VGLUT2 on glutamatergic PV-positive neurons will result in deficits in locomotion not to mention decreased pain sensitivity [55]. In addition, Piezo2 inactivation and Piezo2 channelopathy-associated GABA release in the dorsal root ganglion during exercise could also leave the entrainment of VGLUT2-expressing PV positive Type II afferents to hippocampal PV-positive GABAergic pacemaker cells unparalleled by VGLUT2-containing Type Ia fibers. It is interesting to note that conditional knockout VGLUT2 mice showed substantially different oscillatory activity in the hippocampal C3 region especially considering the impaired spatial memory of these animals [56].

The current author theorizes that proton–proton frequency coupling through VGLUT2 may provide the ultrafast long-range signaling pathway for the proposed synchronization of the oscillation of proprioceptive afferent terminals with TR. Protons are recognized as fast neurotransmitters of the CNS [57]. In addition, protons control vesicular glutamate transporter proteins, that are proton- and voltage-activated channels, through allosteric transmission regulation at a distance [58]. However, VGLUTs are organic anion transporters [59], but they also act as proton–glutamate antiports [60]. It is said that "protons are fast and smart" while "proteins are slow and dump" [61]. Fuller et al. rightly suggested quantum tunneling as a potential mechanism [52] for the suggested ultrafast signaling. Proton tunneling is one form of quantum tunneling, leading to the ultrafast disappearance of a proton at one locus and the appearance of the identical proton at another nearby locus, separated by a barrier. The referred ultrafast signaling pathway with VGLUT2 representation, as proton semiconductors in the CNS, could include the following: DRG of proprioceptive afferents [52]–dorsal column medial lemniscus (spinal conscious proprioceptive pathway) [55]–hypothalamus habenula [52,62,63]–thalamus [64]–hippocampus [55].

It is important to note that VGLUT2 might have a role in unconscious proprioception as well, since diffuse TBI induces the susceptibility of Purkinje cells due to long-range neuronal circuit disruption [65]. It is noticeable as a consequence that VGLUT2 synaptic density is substantially reduced in the cerebellum one week after TBI [65]. Another indication is that cerebellar Purkinje cells also express Piezo2 [17].

Furthermore, when Piezo2 inactivates at baroreceptors, then the $Ca_v1.3$ is proposed to be the critical ion channel pacing the heart rhythm controlling pacemaker cells in cardiac sympathetic activation [5,15]. The current author suggests that they also synchronize to hippocampal TR. Hence, the intensity-dependent increasing frequency could be driven by these L-type $Ca_v1.3$ channels containing pacemaker cells in order to entrain to hippocampal GABAergic pacemaker cells through their electrical resonance. Indeed, $Ca_v1.3$ channels are shown to be generators of spontaneous oscillations [66] and capable of mediating subthreshold resonance on GABAergic neurons [67]. L-type channels are clustered at the base of major hippocampal pyramidal neurons' dendrites [68]. It is theorized that TR has a role in the coding of speed, Several studies demonstrated the speed-dependent frequency, amplitude of TR and the synchronization of TR with running speed [3]. This speed-dependent coding could be a calculated derivate signaling from L-type and Piezo2 channels. Accordingly, Piezo2 might have a role in speed detection by providing a signal input from resonant frequency excited by velocity. Piezo2 is involved in vibration detection as well, supporting this theory [69].

3.3. Rapid Eye Movement

Another interesting Piezo2-coupled synchronization moment might be the rapid eye movement (REM) during sleep. REM sleep consistently and characteristically shows TR [70]. REM sleep is induced by autogenic ponto-geniculo-occipital waves. The abrupt activation of these rapid eye movements stretches extraocular muscle (EOM) spindles, hence activating Piezo2 on primary afferent terminals. It is noteworthy that EOMs have special metabolic and ionotropic characteristics that rather resemble lower vertebrates or denervated mammalian muscles, like acetylcholine contractures [71]. As theorized earlier, entrained Piezo2 activation initiates synchronization to TR ON by MS glutamatergic neurons with the underlying pacemaking of PV-expressing GABAergic neurons. Eye movements during REM sleep are predominantly vertical [72]. The inhibitory neurotransmitter for the premotor neurons contributing to vertical eye movements is GABA and that contributing to horizontal eye movement is glycine [73]. It is notable that the involved agonist and antagonist EOMs are countermodulated. When REM sleep is induced by autogenic ponto-geniculo-occipital oscillation, then the Piezo2 content of the involved repetitively stretched muscle spindles of the EOMs, involved in the vertical vestibulo-ocular reflex, could provide the hippocampal TR turn-ON by MS glutamatergic neurons through Piezo2 coupling. Glutamatergic neurons participate in the excitatory neuronal circuitry of REM sleep, while glycinergic neurons provide the inhibitory hyperpolarization [13]. These modulations could explain the vertical movement dominance of EOMs during REM sleep. However, the question rightly addressed how these EOMs are not experiencing reversible atonia in contrast to the rest of the muscles during REM sleep [13]. It is noteworthy that GABAergic neurons control the REM-atonia neurons contributing to the reversible motor paralysis during REM sleep [13]. The aforementioned EOM contractions, likely driven by acetylcholine release, are enhanced by REM sleep and facilitate the bypass of the GABAergic inhibition. Interestingly, EOMs are relatively preserved in ALS, and it is theorized that the increased Wnt signaling in EOMs may spare adequate Piezo2 gating control through the sufficient level of PIP2 stimulation [10,74]. Furthermore, PIP2 decrease could induce GABA-activated GIRK current inhibition [75]. GIRK channel activation is an important mechanism during REM sleep, because it could decrease the excitability of motoneurons [76]. Hence, it could be one explanation regarding how EOMs are preserved in ALS. Since Wnt signaling, PIP2 and reversible phosphorylation are central players of the regulation of circadian rhythm, these mechanisms could provide another explanation for the reversible motor paralysis experienced during REM sleep.

Correspondingly, the LF power component of HRV is significantly higher during REM sleep compared to non-REM sleep [77]. In support of the current novel theory, the abrupt surges of heart rate during REM are entrained to the increased episodes and frequency of theta waves, REM inducing ponto-geniculo-occipital waves and rapid eye movements [78].

In summary, the aforementioned Piezo2 initiated ultrafast signaling and synchronization to TR would explain a lot more about the mystery of proprioception. Correspondingly, TR acts like a central hub by integrating several functions and behaviors within the CNS, but it could be also involved in central background integration and the maintenance of whole-body postural control, locomotion and the orthostatic control of the autonomic nervous system through this novel ultrafast coupling. This background hippocampal integration may have special relevance and sophistication in humans due to the erection to bipedal locomotion and cognitive demand-induced voluntary task execution.

4. Theta Dysfunction and the Theoretical Dysregulated Synchronization with the Piezo System

DOMS is defined by the acute compression axonopathy theory, as the superposition of compression forces may microdamage proprioceptive terminals when unaccustomed or strenuous repetitive eccentric contractions are executed under a cognitive demand-derived ASR [21]. It is noteworthy that unaccustomed also means environmental novelty and the enhanced loading of conscious proprioception. It is noteworthy that environmental

novelty skews theta to a later phase of firing, while a familiar environment skews theta to an earlier phase [79]. Furthermore, eccentric exercise increases cortical activity in addition to increased TR power correlation with task complexity and focused attention [80]. Last but not least, cognitive demand-derived ASR could also have roots in the hippocampus, since the hippocampus is associated with cognition. In addition, arousal, stress regulation and anxiety have been also linked to the hippocampus for a long time [3], and a direct link between stress signals and hippocampal theta was identified [81]. The role of circulating osteocalcin is theorized as an ASR inducer in the aforementioned DOMS theory [21]. Indeed, osteocalcin-expressing neurons are present in the hippocampus, and they are suppressing anxiety [82], as is demonstrated through exercise [83]. Moreover, osteocalcin is known to facilitate spatial learning but also have a role in embryonic development and age-related cognitive decline [84]. It is noteworthy that neural stem cells can sense excitatory neural activity through L-type Ca^{2+} channels and NMDA receptors; this neuronal excitation induces changes in gene expression and neurogenesis [85], and osteocalcin might have role in the initiation of this mechanism.

Acute intensive exercise not only intensifies the firing of hippocampal neurons and modulates hippocampal TR but also shows transient neuronal activation by the expression of immediate early genes [3]. Moreover, physical exercise shows increased activation of immediate early genes only in the hippocampus and not in other parts of the brain [3]. It is remarkable that Piezo2 is present in the hippocampus [17] and Piezo2 channelopathy is theorized to be a principal transcription activator [14], providing further support to the current theory.

It is theorized that similar neuron terminal microinjury could develop in diabetes mellitus, such as the one proposed in DOMS [21]. The usage of this analogy may be permissive despite the profound differences upstream between these insults [86]. Correspondingly, abnormal diastolic blood pressure and heart rate is a consequence of tilting in diabetes mellitus, indicating an impaired autonomous nervous system [87]. A recent observation confirms these perturbations in DOMS as well, which was demonstrated by an acute intensive exercise protocol combined with an isometric wall-sit and followed by an orthostasis test [88]. Indeed, atypical hippocampal-like metabotropic PLD-mGluR is homomeric to metabotropic GluK2 [32], and GluK2 is involved in the maintenance of glucose homeostasis [89]. Moreover, mGluRs in association with GABA are involved in glucose-stimulated insulin secretion in the beta cells of pancreas [90], and Piezo1 plays a critical role in this process [91]. Hyperglycemia is associated with reduced HRV and reduced LF power in diabetic subjects [92]. LF power is also decreased in mTBI [93]. In support of the current theory, hyperglycemia alters TR and causes working and spatial memory impairments along with hippocampal learning and memory properties [94]. A parallel of the spatial learning deficit could be observed in mTBI too as defective alterations in hippocampal theta, which are represented in reduced theta power and theta frequency [95].

DOMS not only delays the static phase firing encoding of the stretch reflex [40], likely due to the switch [8] or miswiring of proprioception [14,20], but also induces mechanical hyperalgesia [15]. The initiating input of this acute neuropathic-like pain is proposed to evolve from this proprioceptive miswiring, leading to the activation of WDR neurons on the spinal dorsal horn through NMDA receptor activation in cahoots with L-type calcium currents and imbalanced subthreshold Piezo2-derived cationic currents [15]. The recent findings of Fuller et al. may support this theory where they found that intact PV positive proprioceptive sensory neurons tonically ablate nociceptor activation at the DRG level. Consequently, the deletion of these neurons induces the activation of nociceptors leading to WDR neuron activation and acute pain [52]. Activated WDR neurons on the spinal dorsal horn have been long implicated in reference to the gate control theory of pain [96,97] like activated NMDA receptors as well [8]. Indeed, L-type channels, namely $Ca_v1.2$ and $Ca_v1.3$, are known to activate these WDR neurons, but $Ca_v1.3$ could turn on the wind-up of pain in association with activated NMDA receptors [98]. Moreover, while the role of WDR neurons is acknowledged in pain sensitization spinally, the loss-of-function mutations in Piezo2 also

mean lost pain sensation and sensitization [69]. Furthermore, the deletion of VGLUT2 not only alters hippocampal oscillations [56] and impairs locomotion but also leads to reduced pain sensitivity [55]. It is important to note again that VGLUT2 is present on both Type Ia and Type II proprioceptors with higher expression on the later one [41]. Accordingly, the lost function of VGLUT2 on Type Ia fibers due to Piezo2 channelopathy could lead to DOMS, as was hypothesized by the acute compression axonopathy theory.

Piezo2 indeed has the synchronizing characteristics and $Ca_v1.3$ has the frequency mediating features supraspinally, and it might be the case spinally as well. Hence, the irreversibly lost function of excitatory Piezo2 in ALS may lead to the theorized lost synchronization of locomotion supported by central pattern generators, not to mention to the lost function of the spinal $Ca_v1.3$ ion channels, leading to the blunt function of WDR neurons and eventually to the painless condition of ALS [15]. In support of this line of thinking, neuropathic pain impairs spatial memory performance [99], and chronic pain increases theta oscillation [100]. It is even more interesting that the higher pain intensity of osteoarthritis comes with lower theta activity in contrast to lower pain intensity when theta oscillation power is higher [101]. It is also important to note that the tertiary injury phase of DOMS is called a repeated bout effect, while in the case of non-contact anterior cruciate ligament injury, the third injury phase is represented in re-injury and osteoarthritis [8,102]. Both conditions are proposed to be initiated by Piezo2 channelopathy [9,102]. This proposed novel mechanism and signaling could be another indication that neuropathic pain indeed needs a triggering peripheral input, likely a Piezo2-based one, for central sensitization [103]. It is important to note that this peripheral pain input is bidirectional in terms of pathophysiology, because pathologically prolonged overstimulation of Piezo1 mechanotransduction could also lead to Piezo2 channelopathy within an affected compartmental milieu, hence constructing a pain spectrum where neuropathic pain is the worst outcome on this spectrum [10].

Finally, Nagi et al. already demonstrated the existence of an ultrafast signaling mechanism in the pain sensation of human skin, but they excluded the involvement of Piezo2 [104]. However, the author of this manuscript suggests that the findings are not contradictory to Piezo2 involvement. Voltage-gated sodium channels participate in mechanotransduction in a secondary fashion if Piezo2 is inactivated [5,20] or lost. However, the resultant bypassing or losing of the low-frequency Shottky barrier semiconductor diode function of Piezo2 could also mean diminished control of fine movements or fine touch with preserved ultrafast proton- or voltage-based VGLUT2 signaling on the DRG level. One example for this is when the LF power of HRV drops to almost undetectable level during acute intensive exercise. As a consequence, Piezo2 is suggested to be inactivated [5], and the control of fine movements is minimized in order to trade it for the ASR or allostasis, as was theorized in the acute compression axonopathy theory of DOMS [21]. This is when most likely Na_v channels take over the control of proprioception in a secondary fashion on primary afferents but in a diminished way.

In summary, the current author suggests that Piezo2 provides access not only the synchronization to TR but also the fine grading to the aforementioned ultrafast signaling through its Shottky diode function.

5. Conclusions

The current paper puts into perspective a novel ultrafast resonance-based cross-frequency coupled communication that could provide peripheral spatial-, speed-inputs to the space- and speed-coding of hippocampal TR, supporting postural control to locomotion and episodic memory. This novel signaling function would add in the future to the evidence supported by research that Piezo2 not only participates in detection of indentation, compression, stretch, shear stress, and vibration, as well as participating in neuronal cell homeostasis maintenance and proprioception, but also contributes to whole-body organizational control by an ultrafast signaling that is faster than a neurotransmitter-based one. Furthermore, it could add to recent theoretical functions of Piezo2, like being the primary

damage and principal transcription activator when they experience a channelopathy [14]. Moreover, it could be the fourth and fifth direct (molecular) or indirect (non-molecular) theoretical proof (some of them even research based) of Piezo2 channelopathy, as suggested first in 2021 [9]. The others include miswiring reflected in impaired proprioception [40,75], miswiring induced exaggerated contractions [8,9] or joint contractures [105], peripheral input to neuropathic pain due to miswiring [14], autoimmune conditions and diseases [11,12,16], and now the impaired or lost LF Shottky barrier semiconductor diode function of Piezo2, leading to altered TR.

Moreover, Piezo2 channelopathy could impair this novel ultrafast communication in many conditions and diseases with not entirely known etiology, resulting in impaired proprioception, autonomic disbalance, impaired orthostasis and pain. The LF power of HRV and the power, frequency, and amplitude of hippocampal TR could gain higher diagnostic relevance in the acute, chronic or irreversible form of Piezo2 channelopathy in the future and in many more areas, even in cancer. After all, it does not seem to be an accident that Piezo2 knockout mice cannot survive after birth. The progressive irreversible functional loss of these channels is theorized to be the underlying cause of the lethality of ALS [13], likely revealing the principality of these channels in the most profound way through this lethal disease. Last but not least, the current theoretical model might be permissive because the mysterious mechanostransductory function of Piezo ion channels, especially Piezo2, may require a whole body, multi- and interdisciplinary approach; otherwise, it could be hardly understood. Finally, looking only at biology and not considering physics concomitantly is not helping an in-depth understanding, because mechanotransduction is the conversion of physical cues to biological signals, and it is indispensable for life sustainment.

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