Concept Paper

Position Sense, Proprioception, Memory in Light of Piezo2 Channelopathy as Traumatic Brain Injury and Alzheimer's Disease Show

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Position Sense, Proprioception, Memory in Light of Piezo2 Channelopathy as Traumatic Brain Injury and Alzheimer's Disease Show

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Abstract

Recent re-examination of the gravity-dependency of position sense revealed two distinctive proprioceptive pathway generation. One was indeed gravity-dependent as matching and pointing tasks showed, while the other one was suggested to use memory as repositioning demonstrated it in a gravity-independent fashion. The current manuscript puts forward that not only matching and pointing tasks use muscle spindle-dependent position sense, but repositioning as well. Consequently, memory-supported repositioning does not involve peripheral proprioceptor encoding acutely in the context of scene representations, however spatial and episodic memory with critical hippocampal contribution may essentially rely on earlier peripheral intrafusal proprioceptive Piezo2-initiated input source through hippocampal learning and memory. Furthermore, the cingulate cortex and working memory may be involved in this memory process downstream. Accordingly, the underlying proposed two distinctive proprioceptive pathways are the following: the muscle spindle-derived proprioceptive terminal Piezo2-initiated ultrafast signaling may contribute to motoneurons in a monosynaptic fashion through VGLUT1 and to the hippocampus as well through VGLUT2. Delayed onset muscle soreness, with the theorized microdamage of these proprioceptive terminals, impairs the efficiency of proprioceptive integration and body representation process during body-related motor imagery. Body representation is indeed crucial in spatial, episodic and working memory formation. This manuscript puts into perspective how the microdamage of Piezo2 on these proprioceptive terminals may not only miswire proprioception acutely, like in delayed onset muscle soreness, but with chronification as well, leading to spatial, episodic and working memory impairments, and rapid eye movement sleep reduction. This longitudinal trajectory is demonstrated mainly though traumatic brain injury and Alzheimer's disease.

Keywords: position sense; gravity; proprioception; memory; Piezo2 channelopathy

1. Introduction

The re-examination of the gravity-dependency of position sense resulted in indispensable findings, namely the confirmation of the gravity-dependency of matching and pointing tasks, in contrast to repositioning where gravity had no impact [1]. In addition, Proske and Weber found that the position sense of repositioning is independent of peripheral sensory receptors' contribution, in contrast to muscle spindle-dependent position sense of matching and pointing tasks [1]. These observations implied two pathways in proprioception generation, and repositioning was suggested to use memory along one of these pathways [1]. The current author is in agreement with the two distinctive pathways, however posits that repositioning also uses contributions from peripheral

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sensory receptors, but from earlier that is consolidated in spatial and episodic memory through hippocampal learning and memory, and possibly involving other brain regions, like the cingulate cortex (CC) and its role in working memory. Moreover, the two distinctive peripheral pathways relying on proprioceptive sensory receptors-induced ultrafast signaling (Table 1) provide the sensory feedback to lower motoneurons instantaneously and to upper motoneurons with the involvement of consolidated memory.

1. Two Distinctive Proprioceptive Pathways and Memory

Notable that anterior CC has a critical role in working memory as a traumatic brain injury (TBI) study showed [2]. TBI also increases reaction time and lowers response accuracy of spatial working memory tasks [2]. The deletion of PIEZO2, resulting in Piezo2 loss of function, increases escape latency during the defensive arousal response in TBI [3], not to mention it reveals a body-wide Piezo2 system [4]. Moreover, the activity of the left sensimotor cortex is decreased with increased task difficulty in TBI, hence reflecting additional challenge since this brain region is the one that compensates for the diminished executive function of the anterior CC in TBI [2].

Piezo2 is considered as the principal mechanosensory ion channel responsible for proprioception [5]. The team of Nobel laureate Ardem Patapoutian may have coined the principality of Piezo2 in proprioception too early [5], because later other genetic knock-out models in reference to other ion channels, like ASIC3, $Na_v1.1$ and ASIC2, also resulted in proprioceptive impairments. In support of Piezo2's proprioceptive principality, it was proposed in 2023 that muscle spindle-derived proprioceptive terminal Piezo2-initiated ultrafast signaling not only contributes to motoneurons in a monosynaptic fashion through vesicular glutamate transporter 1 (VGLUT1), but to the hippocampus as well through VGLUT2 [6] on top of a hierarchy of mechanotransduction under ultradian events [4] (Figure 1).

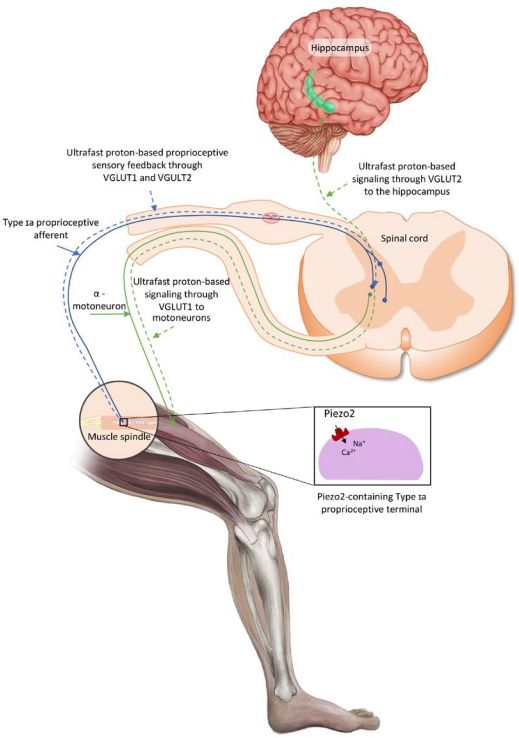

Figure 1. Proposed intrafusal proprioceptive terminal Piezo2-initiated ultrafast proton-based long-range synchronization to hippocampal theta rhythm through VGLUT2 and neurotransmission to motoneurons through VGLUT1 —the current figure is an English adaption of the figure from *Hungarian Rheumatology* [4].

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As a test of this ultrafast Piezo2-initated signaling theory, it was indeed confirmed later in a genetic knock-out study that re-examined sensory neurons in the absence of PIEZO2 and surprisingly found that the inducement of rapidly adapting mechanosensitive currents with very fast activation, and inactivation, were reduced [7]. Moreover, it has been implied in a forced lengthening/eccentric exercise induced delayed-onset muscle soreness (DOMS) related research in 2022 that acquired Piezo2 channelopathy on muscle spindle-based Type Ia proprioceptive terminals may contribute to the delayed latency of the medium latency response (MLR) of the stretch reflex [8]. This Piezo2 microdamage may impair the aforementioned ultrafast signaling and switch of this signaling to the secondary Type II proprioceptive afferents [4,8]. However, this delayed latency may induce a mismatch in between lower and upper motoneurons on neuromuscular junctions due the impairment of the above mentioned two distinct pathways in proprioception generation.

The acute transient indication of this eccentric exercise-induced neural microdamage is not only the increased M-wave latency on motoneurons[9], but even more importantly, it has been proposed that intrafusal proprioceptive Type Ia fibers may be damaged precedingly due to acute Piezo2 channeloapthy-induced VGLUT1 disconnection on motoneurons, represented in the delayed latency of MLR [4,8]. Noteworthy, that eccentric contractions support the body against gravity and it is known that they damage proprioception if prolonged or induce DOMS when unaccustomed [10].

Another longitudinal indication of this neural microdamage that in an amyotrophic lateral sclerosis (ALS) mouse model it was shown that dysfunctional abnormalities could be detected first on neuromuscular junctions, and postsynaptic structural detachment from the neuromuscular junctions happened only subsequently [11]. All of these alterations were present prior to motor symptoms developed [11]. This longitudinal observation is important because the pathophysiology onset of ALS is devoted to age-dependent irreversible Piezo2 channelpathy in the presence of genetic and/or environmental risk factors, proposed first in 2022 and indirectly confirmed in later genetic analyses in 2023 and 2025 [12]. The current author proposes that the neurodegeneration of the aforementioned two distinctive pathways, detected by Proske and Weber, may explain the pathophysiology onset why both lower and upper motoneurons are affected in ALS by dye-back mechanism, and why gravity could be an etiological factor in ALS [13].

Accordingly, the proposed memory-supported gravity independent proprioceptive input source to upper motoneurons may essentially rely on earlier position sense contributions from muscle spindle-based peripheral proprioceptors consolidated in memory. The author of this perspectives manuscript suggests that phantom limb sensations of amputated limbs, and phantom limb pain as well, may be another indication for the existence of this memory-supported gravity independent proprioceptive pathway, reflecting memory-supported position sense from earlier intrafusal proprioceptive input, loss of Piezo2 signaling-induced VGLUT1 disconnection and resultant ultrafast pain. Important to note that an ultrafast pain system was detected earlier and the authors of this study excluded the contribution of PIEZO2 [14]. However, it was proposed later that the contribution of PIEZO2 should not be excluded, because in the functional absence of Piezo2, the Na_v and ASIC3 channels may take over the control of proprioception in a secondary fashion, but in a miswired way [6] with $Ca_v1.3$ loading [12,15]. Hence, ultrafast pain may be the direct consequence of lost ultrafast/fine tuning/modulation by Piezo2 [6]. Therefore, phantom limb pain might be the consequence of transected proprioceptive nerve injury on the affected limb with lost Piezo2 modulation at the hippocampal pain center, but left with miswired proprioception and ultrafast pain signaling through other ion channels, like Na_v, and increased low-threshold $Ca_v1.3$ loading due to the lost proton-based ultrafast signaling.

One more consideration is gravity along the two distinctive proprioception generation pathways. Important to note that Piezo2 ion channels on proprioceptive terminals have been theorized to represent a stochastic nonlinear anti-gravity entropic-spring-like mechanics [16] and this theory is partially supported by proven stochastic entropic-spring-like mechanics of Piezo ion channels [17]. Correspondingly, the invaluable work of Proske and his team show that matching and

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pointing tasks may not only use Piezo2-initiated ultrafast signaling, but anti-gravity entropic-spring-like mechanics of proprioceptive Piezo2 as well.

1. Traumatic Brain Injury and Alzheimer's Disease

In contrast, memory-supported repositioning does not involve peripheral proprioceptor Piezo2 acutely in the context of scene representations and it is a gravity-independent task [1]. However spatial and episodic memory with critical hippocampal contribution may essentially rely on earlier peripheral intrafusal proprioceptive Piezo2-initiated input source through hippocampal learning and memory in support of repositioning. A recent study, that used proprioceptive terminal microdamage[8] as a working hypothesis, indeed showed that DOMS impairs the efficiency of proprioceptive integration and body representation processing during body-related motor imagery [18]. Body representation is crucial in spatial [19], episodic [20] and working memory formation, not to mention its role in constructing the body image and body memory [21]. Interestingly, Piezo2-coupled synchronization during rapid eye movement (REM) sleep may contribute to spatial and episodic memory consolidation [6] that might explain why elevated REM sleep duration enhances the accuracy of working memory [22]. Moreover, the altered CC functions in mild TBI[23], the decreased REM sleep in TBI[24] and the alteration in working memory functional activity in mild TBI[25] are devoted principally to the pathophyisiology-initating Piezo2 channelopaty by the current author.

Final consideration that the PIEZO2-influenced defensive arousal response of the aforementioned TBI study [3] has a critical brain locus in the CC when it comes to the initiation of this response. TBI is known to be an established risk factor for Alzheimer's disease (AD), especially with repeated bouts. Notable that irreversible Piezo2 channelopathy has been proposed to be the pathophysiology initiating microdamage in AD as well at the prefrontal cortex in the presence of genetic and environmental risk factors [26]. Accordingly, it is demonstrated that the CC of the prefrontal cortex is an early target of AD pathology [27]. Moreover, it has been long known that the CC is where the earliest and largest energy metabolism reduction takes place in AD [28]. In support, the proposed irreversible Piezo2 channelopathy-induced proton reversal and resultant OXPHOS depletion may explain this energy metabolism switch [4,29] even in AD [26]. After all, irreversible Piezo2 channelopathy-induced lost ultrafast signaling from the prefrontal cortex to the hippocampus might explain the early impairment of hippocampal spatial and episodic, and working memory. Furthermore, irreversible Piezo2 channelopathy may explain the significantly reduced REM sleep in AD [30].

One recent preprint paper highlights that rare coding variant of PIEZO2 indeed implicated in AD disease mechanism [31], while an another preprint emphasizes acquired irreversible Piezo2 channelopathy's relevance in the initiation of AD disease mechanism [32]. Accordingly, the current author proposes that the rare coding variant of PIEZO2 presents an alteration from glutamate to lysine, and since glutamate is negatively charged and lysine is positively, therefore it may cause a critical charge alteration at functionally critical site, leading to age-dependent irreversible Piezo2 channelopathy in the presence of underlying genetic and environmental risk factors.

References

1. Proske, U.; Weber, B.M. Measures of Human Position Sense Do Not Always Include Contributions From Peripheral Sensory Receptors. *Eur J Neurosci* **2026**, *63*, e70444. https://doi.org/10.1111/ejn.70444.
2. Cazalis, F.; Babikian, T.; Giza, C.; Copeland, S.; Hovda, D.; Asarnow, R.F. Pivotal role of anterior cingulate cortex in working memory after traumatic brain injury in youth. *Front Neurol* **2011**, *1*, 158. https://doi.org/10.3389/fneur.2010.00158.
3. Zhang, Q.; Ma, H.; Huo, L.; Wang, S.; Yang, Q.; Ye, Z.; Cao, J.; Wu, S.; Ma, C.; Shang, C. Neural mechanism of trigeminal nerve stimulation recovering defensive arousal responses in traumatic brain injury. *Theranostics* **2025**, *15*, 2315-2337. https://doi.org/10.7150/thno.106323.

 doi:10.20944/preprints202604.1524.v1

4. Sonkodi, B. Acquired Piezo2 Channelopathy is One Principal Gateway to Pathophysiology. *Front Biosci (Landmark Ed)* **2025**, *30*, 33389. https://doi.org/10.31083/FBL33389.
5. Woo, S.H.; Lukacs, V.; de Nooij, J.C.; Zaytseva, D.; Criddle, C.R.; Francisco, A.; Jessell, T.M.; Wilkinson, K.A.; Patapoutian, A. Piezo2 is the principal mechanotransduction channel for proprioception. *Nat Neurosci* **2015**, *18*, 1756-1762. https://doi.org/10.1038/nn.4162.
6. Sonkodi, B. Does Proprioception Involve Synchronization with Theta Rhythms by a Novel Piezo2 Initiated Ultrafast VGLUT2 Signaling? *Biophysica* **2023**, *3*, 695-710.
7. Sanchez-Carranza, O.; Begay, V.; Chakrabarti, S.; Pampols-Perez, M.; Wang, L.; Garcia-Contreras, J.A.; Hammes, A.; Lewin, G.R. Mechanically gated currents in mouse sensory neurons lacking PIEZO2. *Biophys J* **2025**, *124*, 4543-4550. https://doi.org/10.1016/j.bpj.2025.10.042.
8. Sonkodi, B.; Hegedus, A.; Kopper, B.; Berkes, I. Significantly Delayed Medium-Latency Response of the Stretch Reflex in Delayed-Onset Muscle Soreness of the Quadriceps Femoris Muscles Is Indicative of Sensory Neuronal Microdamage. *J Funct Morphol Kinesiol* **2022**, *7*. https://doi.org/10.3390/jfmk7020043.
9. Kouzaki, K.; Nosaka, K.; Ochi, E.; Nakazato, K. Increases in M-wave latency of biceps brachii after elbow flexor eccentric contractions in women. *Eur J Appl Physiol* **2016**, *116*, 939-946. https://doi.org/10.1007/s00421-016-3358-2.
10. Hody, S.; Croisier, J.L.; Bury, T.; Rogister, B.; Leprince, P. Eccentric Muscle Contractions: Risks and Benefits. *Front Physiol* **2019**, *10*, 536. https://doi.org/10.3389/fphys.2019.00536.
11. McIntosh, J.; Mekrouda, I.; Dashti, M.; Giuraniuc, C.V.; Banks, R.W.; Miles, G.B.; Bewick, G.S. Development of abnormalities at the neuromuscular junction in the SOD1-G93A mouse model of ALS: dysfunction then disruption of postsynaptic structure precede overt motor symptoms. *Front Mol Neurosci* **2023**, *16*, 1169075. https://doi.org/10.3389/fnmol.2023.1169075.
12. Sonkodi, B.; Nagy, Z.F.; Keller-Pintér, A.; Klivényi, P.; Molnár, M.J.; Széll, M. Genetic Variants in SDC3, KCNA2, KCNK1, KCNK16, and Heat Shock Transcription Factor-1 Genes: An Exploratory Analysis Supporting the Piezo2 Channelopathy Hypothesis in Amyotrophic Lateral Sclerosis Onset. *International Journal of Molecular Sciences* **2025**, *26*, 10218.
13. Akaishi, T.; Takahashi, T.; Abe, M.; Aoki, M.; Ishii, T. Consideration of gravity as a possible etiological factor in amyotrophic lateral sclerosis. *Med Hypotheses* **2019**, *132*, 109369. https://doi.org/10.1016/j.mehy.2019.109369.
14. Nagi, S.S.; Marshall, A.G.; Makdani, A.; Jarocka, E.; Liljencrantz, J.; Ridderstrom, M.; Shaikh, S.; O'Neill, F.; Saade, D.; Donkervoort, S., et al. An ultrafast system for signaling mechanical pain in human skin. *Sci Adv* **2019**, *5*, eaaw1297. https://doi.org/10.1126/sciadv.aaw1297.
15. Nagy, Z.F.; Sonkodi, B.; Pal, M.; Klivenyi, P.; Szell, M. Likely Pathogenic Variants of Ca(v)1.3 and Na(v)1.1 Encoding Genes in Amyotrophic Lateral Sclerosis Could Elucidate the Dysregulated Pain Pathways. *Biomedicines* **2023**, *11*. https://doi.org/10.3390/biomedicines11030933.
16. Sonkodi, B. Big Bang-like, Wormhole-like Mechanisms, and Piezo2 Within Humans. In *Preprints*, Preprints: 2025; 10.20944/preprints202511.1014.v2.
17. Liu, W.; Zhang, X.; He, Q.; Meng, Y.; Tian, B.; Xiao, B. Spring-like mechanics enable rapid inactivation and stochastic single-channel gating of the mechanically activated PIEZO channel. *Cell Rep* **2025**, *44*, 116615. https://doi.org/10.1016/j.celrep.2025.116615.
18. Scotto, C.R.; Ferrier, C.; Bosquet, L.; Toussaint, L. Exercise-Induced Muscle Soreness Impairs the Efficiency of Proprioceptive Integration and Body Representation Processing. *J Neurophysiol* **2026**, 10.1152/jn.00004.2026. https://doi.org/10.1152/jn.00004.2026.
19. Serino, S.; Di Lernia, D.; Magni, G.; Manenti, P.; De Gasperi, S.; Riva, G.; Repetto, C. Egocentric and Allocentric Spatial Memory for Body Parts: A Virtual Reality Study. *J Cogn* **2024**, *7*, 33. https://doi.org/10.5334/joc.357.
20. Torres-Morales, C.; Cansino, S. Brain representations of space and time in episodic memory: A systematic review and meta-analysis. *Cogn Affect Behav Neurosci* **2024**, *24*, 1-18. https://doi.org/10.3758/s13415-023-01140-1.
21. Repetto, C.; Riva, G. The neuroscience of body memory: Recent findings and conceptual advances. *EXCLI J* **2023**, *22*, 191-206. https://doi.org/10.17179/excli2023-5877.

 doi:10.20944/preprints202604.1524.v1

22. Lau, E.Y.; Wong, M.L.; Lau, K.N.; Hui, F.W.; Tseng, C.H. Rapid-Eye-Movement-Sleep (REM) Associated Enhancement of Working Memory Performance after a Daytime Nap. *PLoS One* **2015**, *10*, e0125752. https://doi.org/10.1371/journal.pone.0125752.
23. Michel, B.F.; Sambuchi, N.; Vogt, B.A. Impact of mild traumatic brain injury on cingulate functions. *Handb Clin Neurol* **2019**, *166*, 151-162. https://doi.org/10.1016/B978-0-444-64196-0.00010-8.
24. Grima, N.; Ponsford, J.; Rajaratnam, S.M.; Mansfield, D.; Pase, M.P. Sleep Disturbances in Traumatic Brain Injury: A Meta-Analysis. *J Clin Sleep Med* **2016**, *12*, 419-428. https://doi.org/10.5664/jcsm.5598.
25. Chen, C.J.; Wu, C.H.; Liao, Y.P.; Hsu, H.L.; Tseng, Y.C.; Liu, H.L.; Chiu, W.T. Working memory in patients with mild traumatic brain injury: functional MR imaging analysis. *Radiology* **2012**, *264*, 844-851. https://doi.org/10.1148/radiol.12112154.
26. Sonkodi, B. The Microbiota-Gut-Brain Axis in Light of the Brain Axes and Dysbiosis Where Piezo2 Is the Critical Initiating Player. *Int J Mol Sci* **2025**, *26*. https://doi.org/10.3390/ijms26157211.
27. Kiani, I.; Mohseni, G.; Hassani, T.; Taghilou, A.; Saligheh Rad, H.; Aghamollaii, V. Posterior cingulate cortex atrophy across the Alzheimer's disease spectrum: A cross-sectional MRI study linking volumetrics to cognitive decline. *J Alzheimers Dis* **2026**, *109*, 972-979. https://doi.org/10.1177/13872877251401612.
28. Valla, J.; Berndt, J.D.; Gonzalez-Lima, F. Energy hypometabolism in posterior cingulate cortex of Alzheimer's patients: superficial laminar cytochrome oxidase associated with disease duration. *J Neurosci* **2001**, *21*, 4923-4930. https://doi.org/10.1523/JNEUROSCI.21-13-04923.2001.
29. Sonkodi, B. Delayed-Onset Muscle Soreness Begins with a Transient Neural Switch. *Int J Mol Sci* **2025**, *26*. https://doi.org/10.3390/ijms26052319.
30. Kegyes-Brassai, A.C.; Pierson-Bartel, R.; Bolla, G.; Kamondi, A.; Horvath, A.A. Disruption of sleep macro- and microstructure in Alzheimer's disease: overlaps between neuropsychology, neurophysiology, and neuroimaging. *Geroscience* **2025**, *47*, 3647-3664. https://doi.org/10.1007/s11357-024-01357-z.
31. Lee, W.P.; Wang, H.; Leung, Y.Y.; Cheng, P.L.; Zheng, W.; Valladares, O.; Chung, W.H.; Kuzma, A.; Naj, A.; Vardajan, B., et al. Rare coding variants from ADSP R5 whole-genome sequencing implicate novel genes in Alzheimer's disease. *PREPRINT (Version 1) available at Research Square* **2026**. https://doi.org/10.21203/rs.3.rs-9013646/v1. https://doi.org/10.21203/rs.3.rs-9013646/v1.
32. Sonkodi, B. Alzheimer's Disease, Piezo2 Channelopathy, Piezo1 Channelopathy and the Body-Wide Piezo2 System. *Preprints* **2026**. https://doi.org/10.20944/preprints202604.0091.v1.