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EDITORIAL

# On the Principle and Value of Test Signaling ("Pinging") in Pain Pathways: A Part of an Overarching Principle in Psychophysical Phenomena?

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In any communication system – such as the transmission of a pain signal – it is critical to know if the absence of a signal is an accurate indication of the absence of information to transmit (eg, no pain) or is instead the result of some disruption in the signaling pathway in the presence of information to transmit. An example of such a dilemma occurs when a group of military paratroopers land in the darkness of night. Does the absence of sound mean all is well (other paratroopers are nearby, safe, and on-guard), or the opposite? The question is answered by periodically sending a short, distinct, discreet test signal, ie, a "ping", and waiting for a reply. Computer networks, including the Internet, use the same technique to verify the active/online presence of servers, repeaters, and routers, etc. The knowledge gained differs from the information that is transmitted along the communication system, as it merely ascertains whether the system is intact and functional, or not.

In the case of the transmission of a pain signal, does the absence of an action potential in a postsynaptic neuron in a pain pathway mean that there is no pain, or does it mean that there is some defect in presynaptic, synaptic, or postsynaptic functioning (eg, in transmembrane potential difference, vesicular storage or transport, ion flux, receptor level, or 2$^{nd}$-messenger transduction process)? If the latter, the absence of a pain signal can be detrimental in the short-term (eg, in a potentially fatal incorrect fight-or-flight decision) or long-term (eg, masking a chronic medical condition requiring attention).

To satisfy the requirements and value of a test signal "ping", it must be sent along the same communication, ie, pain transmission, pathway, but must not be confused with an actual signal, ie, the presence of pain. It must be periodic, but not excessively frequent, smaller in magnitude than a full signal so as not to be misinterpreted as a message, and not misinterpreted as "noise" in the system.

In nervous system pathways, these requirements are met by the periodic spontaneous release of a quanta of neurotransmitter release ("quantal packets") from the presynaptic neuron,[1] as originally described by Bernard Katz et al.[2–4] The quantity that is released is very small compared to the amount released during action potential firing (typically the amount contained within a single presynaptic vesicle; for a detailed discussion see, eg, Scimemi & Beato[5]), with much lower frequency (on the order of 0.01–0.03 Hz),[6–9] and is distinguishable and independent from action-potential evoked neurotransmission.[9] Single- or multi-channel parallel signaling is a common engineering feature designed into communication networks – a feature which serves valuable connectivity and quality control functions.[10,11]

An example of another psychophysical phenomenon that, albeit unrelated, suggests that the case of test signaling in pain pathways is part of a more overarching principle, is ocular microsaccades[12] – small eye movements that occur at a frequency of about 1–2 Hz,[13] and mitigate the "Troxler effect" (or "Troxler fading"), which was first discovered by the Swiss physician Ignaz Paul Vital Troxler in 1804.[14] The Troxler effect describes an optical illusion affecting the visual

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perception of peripheral unchanging stimuli/objects that will fade away/disappear from awareness within seconds if current fixation is maintained. Although this may support concentration and avoidance of distractions, without periodic sampling of the periphery this could have negative consequences (eg, loss of situational awareness) – unless the fading is counteracted/mitigated. Martinez-Conde et al[15] stated it succinctly:

> So, our visual system has a built-in paradox – we must fix our gaze to inspect the minute details of our world, but if we were to fixate perfectly, the entire world would fade from view.

Whereas changing the gaze direction or fixation location naturally will trigger a retinal image *change*, fixational eye movements (ie, small eyeball displacements) – akin to the above-described "ping" – *prevent* the fading of peripheral vision during fixation through a retinal image *refresh*.[16]

There are three categories of fixational eye movements: tremor (the smallest, with amplitudes about the diameter of a single photoreceptor), drifts (slow irregular motions of less than two degrees of arc per second), and microsaccades (the largest).[13,17,18] Interestingly, subjects are mostly unaware of their microsaccades, and curiously, despite all three fixational eye movements, perception remains stable. Ongoing research suggests that aspects of this perceptual phenomenon occur in the visual cortex, rather than in the retina.[12]

It would seem, therefore, that the "built-in paradox" described by Martinez-Conde et al[15] could possibly be (re-) interpreted again, at least in part, in the context of the same or similar overarching principle seemingly inherent also in pain pathways, namely the necessity of periodic test-signaling ("pinging" through fixational eye movements, particularly microsaccades) along a common channel (ie, the visual pathway) to warrant/maintain the functionality and fidelity of the communication system (ie, the visual system). The associated characteristics again are: periodic occurrence with non-excessive frequency (around 1–2 Hz for microsaccades),[13] smaller in magnitude than a full signal (ie, small momentary eye displacements causing a retinal image refresh while maintaining fixation),[16] and being distinguishable and independent from "noise" in the system and the main signal (ie, maintaining stable perception despite fixational eye movements vs retinal image changes due to actual/deliberate gaze/fixation changes).[12]

In conclusion, the transmission of signals along pain pathways would be erratic and unreliable without "pinging", and having these associated characteristics. Pain transmission along pain pathways in the absence of an overarching principle of test signaling ("pinging") would likely increase uncertainty and pose an evolutionary disadvantage.

## Disclosure

The authors report no conflicts of interest in this work.

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