

# Potential role of noise to improve intracortical microstimulation in tactile neuroprostheses

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The intracortical microstimulation (ICMS) from 40 to 100  $\mu\text{A}$  is useful to elicit tactile sensations, which could be employed in neuroprostheses to control the robotic arms' movement. However, this electrical current applied for prolonged periods of time could damage the neuronal tissue. Therefore, there is a necessity to create new strategies for the practical use of ICMS in a safe intensity range for potential clinical applications in tetraplegic patients. Here we describe crucial studies supporting the use of electrical and optical noise to guarantee a safe ICMS delivered through brain-machine interface technologies.

Flesher et al. (2016) and Armenta Salas et al. (2018) demonstrated that the ICMS of the human somatosensory cortex elicits natural tactile sensations. In particular, Armenta Salas et al. (2018) successfully restored the lost tactile and proprioceptive sensations in a tetraplegic patient by directly activating somatosensory neurons in the brain. They applied ICMS with a current up to 100  $\mu\text{A}$ , in line with previous studies showing that above 100  $\mu\text{A}$ , there is significant damage in neural tissues by the ICMS (Chen et al., 2014). The specific range of ICMS intensities varied from 40 to 100  $\mu\text{A}$  to elicit a variety of sensations as "squeeze," "tap," "right movement," "vibration," "blowing," "forward movement," "pinch," "press," "upward movement" and "goosebumps." However, such a microstimulation range could be problematic if intracortical electrodes and stimulated neurons need to remain viable for years. This is an essential limitation because a low range of safe intracortical microstimulation intensities during many years could also affect the dynamic range of evoked sensations (Kim et al., 2015). Therefore, it will be necessary to develop new strategies to allow the practical use of ICMS in a low-

intensity range (Medina et al., 2012; Kim et al., 2015). Among such strategies, we suggest that the electrical and optical noise could improve the effects of ICMS in neuroprostheses to control the robotic arms' movement.

Medina et al. (2012) demonstrated the potential role of noise in the improvement of ICMS in primates, following previous findings that the noise could improve somatosensory detection and discrimination (Collins et al., 1996; Lak et al., 2008, 2010). Specifically, Medina et al. (2012) implanted in rhesus monkeys two pairs of ICMS-electrodes separated by 1 mm on the somatosensory cortex. One pair of ICMS electrodes were used to elicit an "artificial tactile sensation." In contrast, the other electrodes were employed to apply aperiodic ICMS of randomly chosen amplitude (i.e., ICMS noise). Here, it is relevant to mention that the term "artificial tactile sensation" was inferred by the psychophysical response of two rhesus monkeys, who sought a virtual object associated with an artificial texture signaled by an ICMS pattern (Medina et al., 2012). Therefore, the experimenters did not directly obtain the subjective quality of the tactile sensation from the monkeys. Conversely, humans are the only ones who can directly report the subjective quality of tactile sensations (Flesher et al., 2016; Armenta Salas et al., 2018). This is the main issue in inferring the sensations felt in animal studies.

Medina et al. (2012) found that the application of moderate ICMS-noise to the primary somatosensory cortex improved the "artificial tactile sensation" produced by the ICMS. This finding strongly suggests that the electrical noise applied to the somatosensory cortex could be employed in the future in humans to improve the tactile perception and augmentation of brain

function via brain-machine interfaces. Therefore, noise could be administered to the cerebral cortex to enhance prosthetic sensations generated by ICMS.

From a gross perspective, Terney et al. (2008) examined the potential long-term effects of transcranial random noise stimulation, showing that it is useful to improve transcranial magnetic stimulation in humans. These authors demonstrated that 10 minutes of transcranial random noise stimulation continuously administered on the primary motor cortex increases the amplitude of motor evoked potentials elicited by transcranial magnetic stimulation. In this case, the administered electrical noise was white noise and it was enough to generate for about 1-hour improvements on transcranial magnetic stimulation via increased excitability in the brain.

In analogy with this gross scheme, Remedios et al. (2019), examined possible mechanisms about the impact of electrical noise in neurons, but in a reduced preparation. They administered short-term random noise electrical stimulation directly applied on isolated pyramidal neurons from the rat somatosensory cortex and applied voltage-clamp ramps to elicit  $\text{Na}^+$  currents. These authors observed that during the electrical random noise electrical stimulation, there is a concomitant augmentation of the  $\text{Na}^+$  current peak-amplitude.

In the same way, Huidobro et al. (2018) applied Brownian optogenetic noise photostimulation (BONP) on the barrel cortex of transgenic mice that expressed channelrhodopsin-2 (Thy1-ChR2-YFP). They found that BONP increases the spike firing responses elicited by mechanical stimulation of such animals' vibrissae. Recently, Mabil et al. (2020) replicated the experiments by Remedios et al. (2019) in Thy1-ChR2-YFP transgenic mice, but using BONP instead of electrical random noise stimulation. They found that BONP was also capable of increasing the amplitude of  $\text{Na}^+$  currents of somatosensory pyramidal neurons elicited by voltage-clamp ramps.

## Perspective

The main point derived from the studies by Remedios et al. (2019) and Mabil et al. (2020) is that low levels of microstimulation could be enough to produce  $\text{Na}^+$  currents of increased amplitude during the administration of electrical or optical noise to the pyramidal cells. Therefore, these findings, together with those obtained by Medina et al. (2012), support electrical and optical noise's feasibility to enhance prosthetic tactile sensations generated by ICMS. For instance, it could be possible that BONP (combined with optogenetics in human pyramidal-neurons) could be added to long-lasting prosthetic interfaces to allow the use of intracortical-electrodes with lower intensity levels of ICMS. This means that noisy light, or noisy electrical stimuli, could be employed to improve the application of ICMS at lower electrical intensities in brain-machine interface technologies (**Figure 1**). However, we must be cautious in extrapolating *in vitro* studies in isolated neurons to the *in vivo* milieu in the human brain, mainly because 1) there are no synaptic connections, and 2) the emergent properties from such networks play a fundamental role in the physiological responses of the brain.

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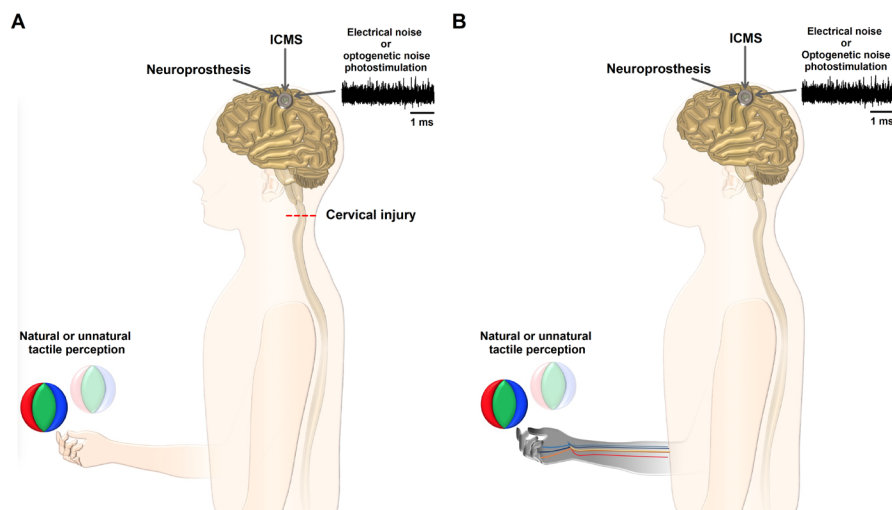
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**Figure 1 | Schemes of the potential role of noise to improve ICMS in tactile neuroprostheses.**

(A) Patient with tetraplegia due to cervical spinal cord injury. (B) Amputee patient controlling a robotic arm through a brain-machine interface. ICMS: Intracortical-microstimulation.

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