Zhou & Zhang. *Zool. Res.* 2023, 44(1): 223−225
https://doi.org/10.24272/j.issn.2095-8137.2022.524

ZR | Zoological Research

Research highlight Open Access

Deciphering neural circuits mediating sound-induced analgesia

Pain is one of the most common clinical symptoms and a leading cause of disability worldwide (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Furthermore, pain is closely associated with various emotional disorders, including anxiety and depression, which may, in turn, heighten pain intensity and prolong its duration (Bair et al., 2003). In previous studies, we identified the neural circuits underlying chronic pain-induced depression and anxiety as well as depression-induced allodynia (Zhou et al., 2019; Zhu et al., 2021). However, due to the complexity of its pathogenesis, therapeutic development remains unsatisfactory, and the discovery of appropriate treatments for pain represents a major and ongoing clinical challenge (Hill et al., 2011).

Music therapy, as a non-pharmacological intervention for pain management, has attracted considerable attention due to its striking analgesic effects, as well as its safety, ease of use, and applicability to many individuals (Lunde et al., 2019). Sound-induced analgesia was reported in dental operations as early as the 1960s (Gardner et al., 1960). Studies have since shown that diverse genres of music, and even sounds from nature, can relieve pain to an equal extent. Thus, the inherent characteristics of music or sound-related environmental factors, that is, not exclusively vocal or instrumental music per se, have been hypothesized to drive these analgesic effects. Functional magnetic resonance imaging (fMRI) in humans exposed to music has revealed changes in the activity of multiple brain areas known to mediate pain processing. However, the neural substrates underpinning the cross-modal audio-somatosensory interactions that may be responsible for sound-induced analgesia remain unclear.

In a recent paper published in *Science* (Zhou et al., 2022), we identified neural circuits that mediate sound-induced analgesia in the brains of mice. To determine whether sound could induce analgesia in mice, we initially delivered consonant sound (e.g., pleasant music for humans) to mice subjected to pain induced by administration of complete Freund's adjuvant (CFA) at sound pressure levels (SPL) of 50 and 60 dB (ambient noise at 45 dB SPL). Surprisingly, only 50 dB sound exposure, but not 60 dB sound exposure, induced analgesia. Next, to determine whether consonant sound harmony was required to induce analgesia in mice, we replaced the consonant sound with dissonant sound (unpleasant music for humans created by electronically modifying consonant excerpts) or white noise, with comparable results obtained for all three sounds. As music-induced analgesia in humans may be attributed to the treatment environment, we conducted pain measurements in the context of different ambient noises and found that the decisive factor in eliciting pain relief was a 5-dB increase in sound intensity relative to ambient noise levels (sound-to-noise ratio, SNR).

We next investigated the neural circuitry through which sound exerts its analgesic effects. Sound signals are collected by the cochlea and then transmitted to the cochlear nucleus, superior olivary, medial geniculate body, and finally to the auditory cortex (ACx). The ACx analyzes perceived signals and subsequently projects to other nuclei to mediate learning, escape behavior, frequency discrimination, and musical pleasure, among others (Schreiner & Winer, 2007). Therefore, we examined the potential role of the ACx in sound-induced analgesia. *In vivo* multi-tetrode recordings showed that 5 dB SNR sound inhibited neuronal activity in the ACx. Chemogenetic inhibition of glutamatergic neurons in the ACx (ACx^{Glu}) significantly increased the nociceptive threshold in inflammatory pain model mice. Furthermore, viral tracing revealed that ACx^{Glu} neurons projected to the posterior (PO) and ventral posterior (VP) nuclei of the somatosensory thalamus, both of which relay nociceptive information.

We then investigated whether these two circuits also participated in 5 dB SNR sound-induced analgesia. Based on

Received: 20 December 2022; Accepted: 29 December 2022; Online: 29 December 2022

Foundation items: This work was supported by the National Key Research and Development Program of China Brain Science and Brain-Like Intelligence Technology (2021ZD0203100) and National Natural Science Foundation of China (32000717)

in vivo microendoscopic calcium imaging, multi-tetrode recordings, and fiber photometry recordings of freely moving mice, we found that PO neurons, but not VP neurons, were rapidly activated by punctate mechanical stimulation of inflamed hindpaws, but not forepaws. Conversely, VP neurons, rather than PO neurons, were rapidly activated by punctate mechanical stimulation of inflamed forepaws, but not hindpaws. In addition, 5 dB SNR sound significantly inhibited the neural activity of PO and VP neurons in mice with inflamed hindpaws or forepaws, respectively. Optogenetic or chemogenetic inhibition of the ACx^{Glu}→PO and ACx^{Glu}→VP circuits mimicked low-SNR sound-induced analgesia in inflamed hindpaws and forepaws, respectively. These results suggest that the observed analgesia induced in mice by the 5 dB SNR sound was mediated by the ACx→PO circuit for hindpaws and ACx→VP circuit for forepaws (Figure 1).

As a man-made, structured sound, music is widely used in all human cultures to express and evoke emotion and promote relaxation and pleasure, although its mechanistic neural basis, especially the neural circuits underpinning sound-induced analgesia, have remained stubbornly elusive. Based on viral tracing, *in vivo* microendoscopic calcium imaging, and multi-tetrode recordings, inhibition of glutamatergic inputs from ACx^{Glu} neurons to the PO and VP mediated sound-induced analgesia in inflamed hindpaws and forepaws, respectively. Furthermore, sound-induced analgesia in mice depended not on melody, but rather intensity relative to ambient noise, consistent with the hypothesis that certain inherent characteristics of sound or contextual factors drive analgesia (Lunde et al., 2019). The neural mechanisms underlying music-induced analgesia in humans are undoubtedly more complex than those revealed in mice (Leknes & Tracey, 2008). Thus, the neural mechanisms driving music-induced analgesia in humans deserve further investigation. Our study expands current understanding of the pathways implicated in the effects of sound in pain processing and may expedite study of music-induced analgesia, ultimately promoting the clinical application of music as an adjunctive treatment for pain.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

W.J.Z. and Z.Z. wrote the draft manuscript. All authors revised, read, and approved the final version of the manuscript.

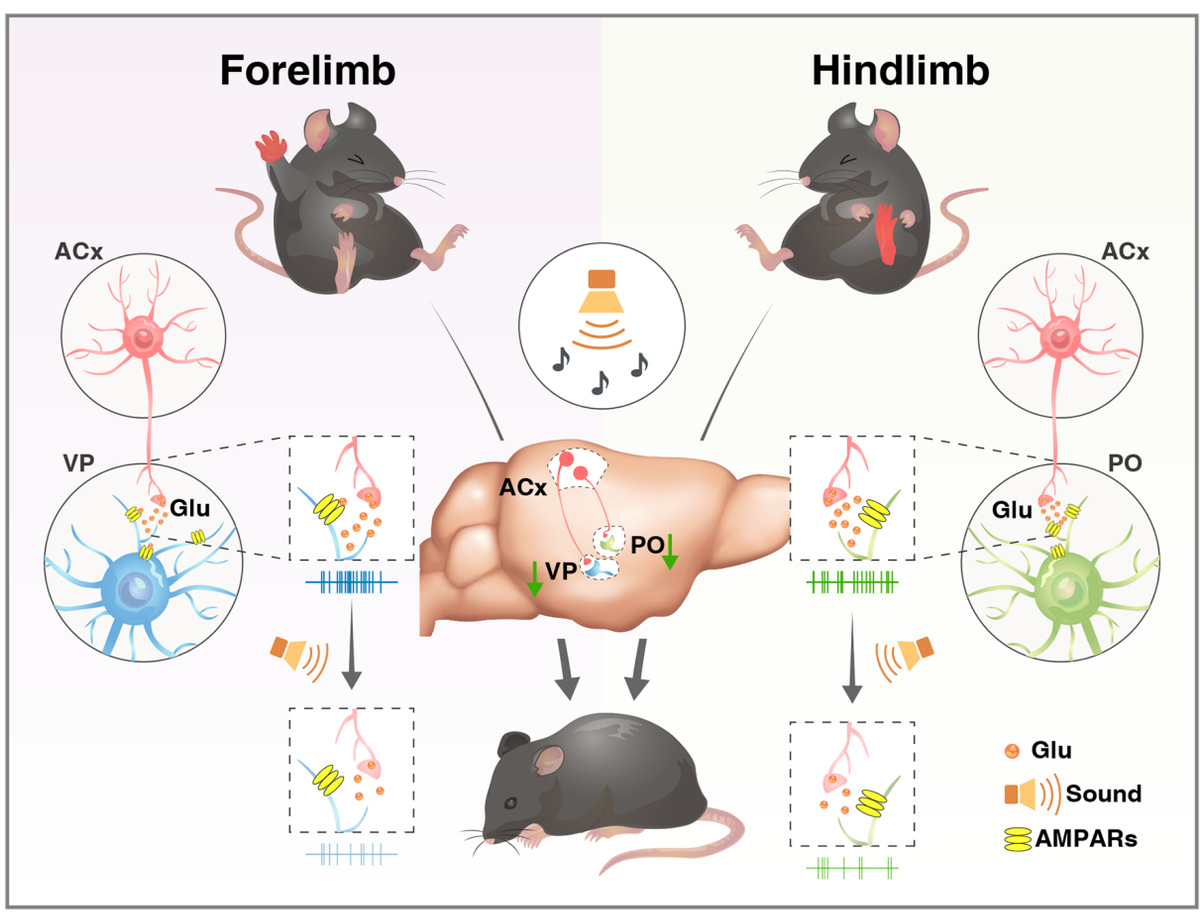

Figure 1 Inhibition of auditory cortex inputs to the somatosensory thalamus drives sound-induced analgesia

Low-SNR sound (music or noise) treatment inhibits excitatory projections from the ACx to PO and VP, thereby reducing excitability of PO and VP neurons and consequently alleviating pain hypersensitivity in inflamed hindpaws and forepaws.

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