ZOOL 567 Topic Summary

The complexity of measuring chronic pain in mice has been widely discussed due to the inability of mice to overtly communicate, and the various types of pain that exist (Kurejova et al., 2010; Mogil, 2009). This review focuses on chronic pain behaviours in mice, such as licking and vocalizing, to assess current expert perspectives on methods for measuring mouse chronic pain.

Common methods for inducing chronic pain in mice include spared nerve injury (SNI), inducing neuropathic pain (pain due to nerve damage), and complete Freund's Adjunct injection (CFA), inducing inflammatory pain (Cobos et al., 2012; Kurejova et al., 2010; Lister et al., 2020; Mogil et al., 2010; Pitzer et al., 2016). Given historic overreliance on reflexive measures of pain, including grimacing, lifting, and licking, many researchers have aimed to demonstrate that these behaviours may be more indicative of hypersensitivity (heightened experience of acute stimuli) than chronic pain (Millecamps et al., 2020; Pitzer et al., 2016; Shepherd & Mohapatra, 2018). Reflexive behaviours are evoked after injury by stimulating the animal and observing the latency of performing one of these behaviours, and are often observed faster and more frequently after induction of chronic pain (Millecamps et al., 2020; Mogil et al., 2010; Pitzer et al., 2016; Shepherd & Mohapatra, 2018).

To test if reflexive behaviours indicate hypersensitivity, researchers sought to develop assays for voluntary behaviours and see if one type of behaviour persisted longer after injury (Cobos et al., 2012; Guo et al., 2019). Many methods for measuring voluntary behaviours have been developed. Place-avoidance involves a mouse choosing between remaining in an aversive brightly lit chamber, or a favorable darker chamber in which the injured limb is mechanically stimulated. Mice with severe chronic pain tend to choose the brightly lit chamber over injury stimulation (Guo et al., 2019; Millecamps et al., 2020; Shepherd & Mohapatra, 2018). To measure changes in physical activity with chronic pain, researchers have also used digital recording to measure activity on a running wheel, climbing, and gait changes (e.g. shorter stride length), demonstrating aversion to physical activity with chronic pain (Cobos et al., 2012; Mogil et al., 2010; Pitzer et al., 2016; Shepherd & Mohapatra, 2018). Some researchers have also been interested in the relationship between chronic pain and social variables such as communication and social interaction. Kurejova et al. (2010) measured increased voluntary ultrasound

vocalizations, the evolved auditory range specific to other mice, using a specialized enclosure and sound recorder as a measure of chronic pain. Piardi et al. (2020) measured the relationship between chronic pain and social interaction by examining the likelihood of (1) developing chronic pain under social isolation and (2) submitting to social isolation while experiencing chronic pain. Socially isolated mice were likely to develop chronic pain due to a minor injury, and chronically injured mice were likely to become socially avoidant after an aggressive interaction (Piardi et al., 2020). Another behavioural measure of chronic pain is hypervigilance to predator odors, which indicates a mouse's recognition of increased predation risk due to its injury, and suggests an evolutionary advantage conferred by chronic pain (Lister et al., 2020). The majority of studies find that voluntary behaviours are a more reliable indication of chronic pain than reflexive behaviours, especially as hypersensitivity appears to persist significantly longer than functional limitations associated with chronic pain (Cobos et al., 2012; Guo et al., 2019; Mogil et al., 2010; Pitzer et al., 2016).

Researchers have indicated that there is need for longitudinal studies which assess reflexive and voluntary behaviours in social and nonsocial mice (Cobos et al., 2012; Kurejova et al., 2010; Millecamps et al., 2020; Shepherd & Mohapatra, 2018). There is also much discussion of stress and chronic pain in mice, however there is little measurement of stress-related hormones in mouse chronic pain models (Guo et al., 2019; Kurejova et al., 2010; Mogil, 2009; Pitzer et al., 2016). Given the strong relevance of hormonal and neurological influences on pain, this may be an important avenue for future research. Finally, as mice are common laboratory animals, research is primarily experimental, not observational, leaving chronic pain behaviours in wild mice essentially undiscussed. As such, chronic pain behaviours in wild mice may be an important avenue for future research.

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