Q10: Can/should we include measures on the affective aspects of OA-associated pain e.g. depression, anxiety etc?

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Response: YES. The affective dimension of pain is the partner to the sensory dimension of pain and represents the emotional 'unpleasantness' or 'aversive' of pain, often leading to desires to end, reduce, or escape from the inciting cause. As such, the affective aspects of pain are part of the definition of pain, and therefore, assessment of OA-associated pain is incomplete without measuring these components.

Level of Evidence: MODERATE

Delegate Vote: Agree: Disagree: Abstain:

Rationale: Negative affect states associated with pain include distress, anxiety, depression, fear, and anger; affect directly modulates sensory processing of pain; and affect itself can be modulated by components like mood, emotion, attention, and learning. Anxiety and depression are commonly comorbid with OA, with a prevalence of 20-40%, and an improved understanding of the negative affective aspects of OA-associated pain could improve the management and treatment of OA in pain for large numbers of people. Functional assessments of the affective components of pain have been carefully evaluated for construct validity in rodent pain models, and many assessments are directly analogous to those used in human pain research. These measures can readily be incorporated into the evaluation of OA-associated pain. While there are few existing reports on the affective aspects of OA-associated pain in rodent models, these aspects provide unique opportunities to assess the role of common covariates in OA pain and to uncover the mechanisms by which comorbidities, such as neuroinflammation, affect OA-associated pain.

The Affective Aspects of Pain are a Component of the Definition of Pain: According to the International Association for the Study of Pain (IASP), pain is 'an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage'.[1] Thus, the affective dimension of pain is the partner to the sensory dimension of pain, and can be separated from this sensory dimension. This negative affective dimension represents the 'unpleasantness' or 'aversive' nature of pain and often leads to desires to end, reduce or escape from the inciting cause. Modification of affect dimensions influences the sensory processing of pain, although the ability to separate the sensory and affective dimensions of pain remains controversial in some areas of the pain community with a large divide between experimental studies and clinical practice, and an evidence base that is not clear cut. [2] Negative affect states associated with pain include distress, anxiety, depression, fear, and anger, and these states themselves can be modulated by components like mood (e.g. catastrophizing), emotion, attention, and learning.[3-5] Importantly, according to the IASP, the inability to communicate verbally does not negate the possibility that a human or nonhuman animal experiences pain,[1] including both the sensory and emotional experience. Therefore, despite the lack of a clear cut evidence base in clinical pain studies,[2] because of the inclusion of affective dimensions in the definition of pain, measures of affective aspects of OA-associated pain should be included, where possible, in evaluation of animal models of OA.

Affective States Influence Pain Processing via Top-Down Modulation and Interoceptive Integration: Interoceptive processing is how the nervous system senses internal signals arising from the body. Two brain regions are responsible for the perception of pain, the lateral and medial systems of the lateral spinothalamic tract. The medial system is involved in processing affective pain responses, attention, and learning and integrates structures including the medial thalamus, the perigenual, midcingulate, and insular cortices.[6] Compared to the lateral pain system, the medial pain system is more active in knee OA pain.[7] Affect modulates pain through descending regulatory systems involving the prefrontal cortex, anterior cingulate cortex, periaqueductal gray, rostral ventromedial medulla, and insula,[8,9] with the amygdala serving as a key hub linking affect and pain.[10] With regard to pain processing in OA, the biopsychosocial framework of pain in humans tries to incorporate both the affective and sensory components of pain, and their levels of integration into a single model,[6] which is logical given the similar anatomic sites of sensory and affective pain processing in OA. Many of these biopsychosocial factors can be effectively modeled in rodent species.

Functional Assessments of the Affective Aspects of Pain have been Carefully Evaluated for Construct Validity in Rodent Models: Many components of negative affect can be assessed in rodent models, when the appropriate level of rigor is used, and this is done routinely across many disease models, and many areas of neuroscience, physiology, and behavior studies. Negative affect can be assessed in preclinical rodent studies through observation of specific species-typical behaviors in response to biological or environmental factors. Caution however is needed in interpreting single-measure outcomes, and multiple test results should be integrated to increase reliability and increase relevance,[11] because for example, anxiety and depression have multiple psychological components, and no single test can capture all facets.[12] While construct validity and translational relevance has been questioned in preclinical models,[13] this has carefully been evaluated using several different frameworks.[13,14] Many behavioral test protocols now commonly used to evaluate anxiety- and depression-like behaviors in rodents have similar or analogous human protocols,[13] and the differences between the responses to the test protocols between rodent and human in different situations or models, as well as the limitations of the testing in rodents are becoming increasingly well understood.[13] Anxiety-related behaviors are most commonly evaluated using the open field test and elevated plus maze, with less frequent evaluation using the light-dark box and elevated zero maze tests. Novelty suppressed feeding tests, and various social approach-avoidance, social interaction, or social approach tests are also commonly used. Depression-related behaviors include learned helplessness to inescapable stress, behavioral despair to forced swim or tail suspension, evaluation of anhedonia via sucrose preference testing, and assessment of cognitive bias through various learning tasks. Therefore, behavioral test protocols have carefully been evaluated in rodents using a variety of disease models across many body systems to evaluate for the negative affect aspects of pain.

Rodent Models of Pain in Osteoarthritis are Associated with Behavioral Responses Consistent with Negative Affect. The majority of the few rodent studies to date that have examined components of negative affect in arthritis pain have used the monoiodoacetate (MIA) injection model. Increases in anxiety-like behaviors have been identified up to 6 weeks after MIA injection; behaviors that were improved by voluntary running wheel exercise, and that were associated with synaptic plasticity changes in the anterior cingulate cortex.[15] Compared with a no exercise group, treadmill exercise was largely protective against development of anxiety-like and depression-like behaviors in mice treated with MIA compared to control untreated mice and was associated with reductions in neuroinflammation.[16] During development of age-related knee OA, high fat fed mice spent less time in open areas of the zero maze, and more time with freezing postures compared to usual chow fed mice, consistent with increases in anxiety-like behaviors, independent of percentage body fat and degree of OA.[17] However, while these and other studies show evidence of a link between depression- and anxiety-like behaviors in rodents, OA pain, and covariates like high fat diet and sedentary behavior, the mechanism(s) and their interactions remain unclear, and the influence of these negative affect states on pain and progression of OA remains largely unknown. However, improved understanding of these states could provide novel targets for treatment and management of OA pain.

OA Pain is Frequently Accompanied by Co-Morbid Affective Components in Human OA Populations: Affective states such as anxiety and depression are commonly comorbid with OA; with a prevalence of around 20-40%. Depression and anxiety exacerbate OA pain and physical limitations, increase poor outcomes,[18,19] and increase direct medical costs.[20] There is a recognized need to improve recognition of psychosocial factors and heterogeneity of patients with OA for comorbidities like anxiety and depression, to enable pain phenotyping and improved management of pain in OA.[21] Therefore, including measures of affective aspects of OA pain in animal models could substantially improve understanding of the pathobiology and pathopsychology of negative affective states in OA and improve translation of pre-clinical research and development of options for treatment.

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