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Imaging of glial cell changes in individuals with chronic low back pain: A commentary on Shraim et al.

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This journal recently published a paper by Shraim et al., entitled “Neuroinflammatory activation in sensory and motor regions of the cortex is related to sensorimotor function in individuals with low back pain maintained by nociplastic mechanisms: a preliminary proof-of-concept study” (Shraim et al., 2024). Using simultaneous positron emission tomography (PET)-functional MR imaging and the radioligand (<sup>18</sup>F)-FEMPA, which binds to the translocator protein (TSPO), this study demonstrated potential glial changes in individuals with chronic low back pain (LBP) located in the primary sensory and motor cortices (S1/M1). Neuroinflammatory glial activation was higher in nociplastic LBP than nociceptive LBP and pain-free groups. This activation was correlated with various markers of sensorimotor functions (e.g., sensitivity to hot/cold stimuli, and intracortical facilitation assessed by TMS) and patient characteristics (e.g., poor sleep, depression, disability, and BMI). This is an ambitious proof-of-concept study, creating new testable hypotheses about the differential mechanisms of distinct types of pain. However, the study has certain limitations that need to be considered. PET targeting 18-kDa TSPO is widely used for localizing inflammation in vivo, but its quantitative interpretation remains uncertain (Nutma et al., 2023). Furthermore, given that the experiment was conducted on a small sample of individuals with LBP, it remains to be established whether these findings can be generalized and specific to a subtype of LBP associated with central sensitization.

Over the last few years, a plethora of works have pointed out the importance of precise pain phenotyping to optimize individual treatments of chronic pain. Clinical (QST, quantification of sensory systems), electrophysiological (high-density EEG-MEG-TMS) and functional imaging (MRI or PET) approaches have proved useful to disclose at the individual level some

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particularities of brain activity associated with different expression of LBP. However, they have rarely been used jointly to assess the contribution of glial cells to this process and to develop models of abnormal brain functioning profiles in LBP. In this sense, the findings from Shraim et al. (2024) may provide a valuable therapeutic basis for treating those with central sensitization resulting in nociplastic LBP by targeting neuroinflammation in S1/M1; but although the study is proof-of-principle study, the sample size is very small, particularly in the nociceptive and nociplastic subgroups ( $N=4$  and  $N=5$ ). A larger sample size is required to confirm whether a causal relationship exists and to describe potentially relevant pathogenetic differences. Another challenge specific to pain biomarker development pertains to the complexity of pain and the impact of individual factors such as sex differences. All participants with nociplastic LBP were female. Studies that do not examine data in both sexes separately risk bias in interpreting the findings, may miss important information, and may have limited generalizability in the purpose of developing brain markers. This brings to question how much can really be said about glial changes carried by pain subtypes vs. other factors.

Growing evidence shows that non-neural cells—~~—i.e.that is,~~ ie.that is, glia, and in particular microglia and astrocytes can play a significant role in modulating neural activity that code the perception of pain. These new data support the existence of “neuroinflammatory signatures” accompanied by neurophysiological changes, and related to clinical characteristics (in particular, with the degree of nociplastic pain and negative affect/depressive feelings) in patients with LBP. Moreover, recent findings revealed associations between increased regional glial activation and altered functional connectivity in patients with LBP, indicating an important link between aberrant neuronal connectivity and neuroinflammation. Thus, the evaluation of functional connectivity should also be considered to better characterize brain organization ~~related to~~ related to LBP.

It has been demonstrated that TSPO can no longer be interpreted as a marker of activated microglia in humans. Nutma et al. (2023) have shown that TSPO expression in human myeloid cells is related to different phenomena than in mice, and that TSPO-PET signals in humans reflect the density of inflammatory cells rather than the activation state. In addition, the lack of microglial specificity for TSPO further complicates the interpretation of the TSPO PET signal, as the source of the increased signal will be partly determined by an ensemble of cells responding to it. Interpretation of previous studies using TSPO ligands needs to be nuanced in ~~the~~ light of these recent findings. TSPO PET comes with numerous limitations and caveats; as such, there is significant interest in developing alternative radioligands with the

capacity to distinguish microgliosis from astrogliosis. Emvalomenos et al. (2024) summarized alternative potential markers for gliosis, and technical advances for monitoring glial changes over time in the context of chronic pain.

In conclusion, the study by Shraim et al. holds potential importance, as it may lead to new studies to fill existing ~~gap~~ gaps in the field regarding the contribution of gliosis to LBP subtypes and identify potential targets for interventions. Future studies should further refine the methodological approach, interpretations and validate the heterogeneity in sensory/motor and glial functions between different LBP phenotypes.

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