AUTHORS' REPLY TO CALL FOR CAUTION IN THE USE OF PAINDETECT TO STRATIFY PATIENTS INTO NEUROPATHIC AND NOCICEPTIVE PAIN WITHOUT ADDITIONAL CLINICAL ASSESSMENT.

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To the Editor:

Thank you very much for the opportunity to reply to the letter from Havsik et al. We are grateful to them for sharing their opinions on the PainDETECT questionnaire and welcome the opportunity to further highlight the advantages and disadvantages of the different tools available for investigating pain characteristics and mechanisms in patients with musculoskeletal disease.

The main aim of our study was to use neuroimaging in order to objectively interrogate the central processing of pain in patients with knee osteoarthritis and to investigate whether or not there was a link between the presence of central sensitisation, determined using fMRI, and outcome following knee replacement surgery.

Whilst the modified PainDETECT questionnaire was used to stratify patients for further investigation of the neuroimaging data, as we outline in our manuscript, it is not possible to demonstrate a clear lesion or disease of the somatosensory system in this patient group, and so we cannot use the term *neuropathic* pain to describe this subgroup of patients (1). Instead we used the term *neuropathic-like* pain in order to reflect the fact that the pain descriptors they use to describe their pain share many features of the pain experienced by patients with neuropathic pain (2, 3). Furthermore, the presence of these features in patients with osteoarthritis has been linked to psychophysical and neuroimaging evidence of central sensitisation (4, 5), and our aim was to further delineate the neural correlates of this process in a new cohort using similar metrics but to additionally determine what, if any, were the consequences of having altered central mechanisms in terms of joint replacement pain outcomes. We fully appreciate the limitation of using the painDETECT questionnaire to stratify patients in this way and, as detailed in our paper, have identified other tools such as the Central Sensitization Inventory and the modified 2010 American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia, developed since the design of the study, which we are keen to use in the future (6-8). Nonetheless, the painDETECT questionnaire has been used to study pain qualities in many different conditions, and indeed its potential use to subgroup patients, according to the pattern of their pain-related sensory abnormalities, in order to make a step towards stratified personalised treatment is being actively investigated with some promising preliminary results (9). In the current study, quantitative sensory testing (QST) was also conducted, in keeping with the 2016 NeuPSIG recommendations (1). This showed a significantly increased sensitivity to cold pain in those with neuropathic-like pain, identified using the modified PainDETECT questionnaire, with a trend towards increased sensitivity for the other QST parameters, but they did not reach statistical significance. In some way, these QST alterations also go towards supporting the groupings we made using PainDETECT, albeit with the caveats regarding its shortcomings that we are in partial agreement with the authors upon.

Hasvik et al rightly point out that the patients with neuropathic-like pain demonstrated important psychological differences compared to the nociceptive group, with increased pain catastrophising and fear of movement. Again, like the QST observations it is nonetheless intriguing that our groupings using PainDETECT cut-offs exposed such differences in psychological mechanisms that we know from our work in neuroimaging (10-13) and other studies (14, 15) significantly contribute to the exacerbation of central sensitisation and chronic pain – i.e. they are part of the combined set of essential mechanisms that contribute to pain amplification/central sensitisation reflected by the neuroimaging differences in the descending pain modulatory system. Finally, it should be noted that although PainDETECT was developed for chronic low back pain and, as such, arguably not transferable to other pain conditions, there is increasing awareness in the chronic pain field that shared underpinning mechanisms exist across chronic pain conditions reflected in some instances, presumably, by shared symptoms. So, similarities are emerging amongst many musculoskeletal

conditions including osteoarthritis, inflammatory arthritis and fibromyalgia (16-18). This paradigm shift in our understanding, where chronic pain conditions are not silos with separate mechanisms and symptoms perhaps captured by distinct questionnaires is reflected in the proposed classification, for the first time, of chronic pain as a disease and diagnosis in its own right for the upcoming 11th revision of the *International Classification of Diseases (ICD).* Here, there is a chronic musculoskeletal sub-category encompassing pain arising from any disease process which directly affects bone, joint, muscle or related soft tissues (19). As we go forwards, it will be interesting to see how together we can harness this classification and tools like neuroimaging and questionnaires to better understand the mechanisms relevant in our patients' pain so that treatments can be better targeted for improved outcomes.

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