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EDITORIAL

Brain Structural Alterations in Chronic Knee Osteoarthritis: What Can Treatment Effects Teach Us?

Osteoarthritis of the knee (KOA), one of the most prevalent causes of pain and disability, is characterized by degradation and loss of articular cartilage, bone overgrowth and attrition, meniscal degeneration, synovitis, and joint capsule thickening. Despite the fact that KOA pathology originates in the knee, the correlation between physical pathology (e.g., knee radiographic findings) and subjective report of the pain experience is at best modest [1], as in other pain conditions such as chronic back pain. The tenuous relationship between peripheral pathology and pain/disability is further illustrated by the fact that a significant proportion of patients (~20% [2,3]) continue to experience significant long-term pain for years after a successful total knee arthroplasty (TKA), that is, even after the presumed resolution of knee pathology. The decoupling of peripheral pathology and pain/disability, as well as the observation that patients with KOA demonstrate hallmarks of central sensitization (e.g., spreading sensitization and temporal summation [4,5]), suggests that central nervous system (CNS) alterations (i.e., neuroplasticity induced by the disorder) may be responsible for the establishment and/or maintenance of persistent pain in this condition. As such, the study of KOA presents excellent opportunities for us to further our understanding of the role the CNS plays in chronic pain, especially in light of the observation that total joint replacement substantially reduces pain symptomatology in the majority of recipients.

The study by Lewis et al. [6] evaluated the occurrence of brain structural changes (i.e., in gray matter volume [GMV] and white matter integrity), as well as changes in psychophysical measures, in patients with KOA, approximately one week before and six months after TKA. Before the surgery, a substantial proportion of patients demonstrated temporal summation (24%) and impaired conditioned pain modulation (38%), which, in agreement with the literature, were significantly rates higher than those of controls (0% and 17%, respectively). These findings are thought to reflect the occurrence of maladaptive central alterations in neural pathways involved in nociceptive processing and modulation. Indeed, structural analyses of the magnetic resonance imaging data revealed that before surgery, compared with healthy controls, patients had smaller GMV in the nucleus accumbens and amygdala, two subcortical regions involved in processing of affective–motivational and other processes, as well as in the ipsilateral primary somatosensory cortex, a cortical region that processes somatosensory information, including pain. This observation is, in broad terms, in agreement with the literature showing that chronic pain is often (although not always) associated with smaller gray matter volume and/or cortical thickness, including in hip or knee osteoarthritis [7,8]. However, it is interesting to note that a recent study in KOA patients [8] found reductions in GMV in a set of brain regions (including orbitofrontal, lateral prefrontal, pre- and postcentral cortices) only minimally overlapping with those reported by Lewis and colleagues. A few factors could contribute to explaining this apparent discrepancy, including differences in methodology and in clinical features of the patients studied in the two studies.

After surgery, patients on average reported a statistically significant reduction in pain. However, consistent with the population prevalence of persistent post-TKA pain, about 20% of them still reported at least mild pain. Notably, TKA also normalized both alterations in temporal summation and conditioned pain modulation, suggesting that surgery and its effects on pain may have reversed some of the central alterations induced by the chronic condition. In fact, of the brain areas demonstrating reduced GMV in the patients preoperatively, the amygdala presented an intriguing pattern when evaluated longitudinally in the patients. After surgery, this region displayed subregions of increased GMV, and no group differences could be detected on the contralateral side in the second scan. A similar pattern of "metric normalization" was observed for the fractional anisotropy (a measurement of the microstructural integrity of the white matter): this measure, which preoperatively was reduced in the midbrain in the KOA group compared with controls, increased in patients after surgery, no longer showing significant group differences.

The significance and interpretation of some of the other longitudinal brain structural changes reported in the study are more uncertain. For instance, a cluster in the ipsilateral primary somatosensory cortex, which presurgically exhibited lower GMV than controls, was no longer significantly different than controls after the surgery; however, a separate cluster in the same functional region, although ostensibly several centimeters away from the former, showed a reduction in GMV compared with the presurgical scan. Moreover, some changes were observed within regions not exhibiting group differences in the presurgical group comparison (e.g., increase in GMV in the hippocampus and periaqueductal gray, or in fractional anisotropy in the corpus callosum and lower brainstem). The fact that these regions were not initially different across groups but demonstrated structural changes after surgery may be reflective of an effect of

surgery itself (and/or anesthesia) on the brain, rather than of chronic pain. Because anesthesia/surgery is associated with adverse effects on cognition (such as delirium and postsurgical cognitive decline), these results may be of interest in this context. It is also noteworthy that no significant correlations were observed between structural brain changes and changes in knee pain or QST measures, suggesting that an array of distinct mechanisms may contribute to treatment-related changes in KOA.

Although not of all of the findings from this paper are easily interpretable, the restoration of GMV in the amygdala and of fractional anisotropy in the midbrain are altogether in agreement with other studies showing that at least some of the brain alterations associated with chronic pain can be reversed by successful treatment [7,9]. Although intriguing and ultimately encouraging for patients suffering from chronic pain, these findings also raise a set of fundamental questions: What are the biological underpinnings of brain structural alterations often reported in chronic pain? What are the mechanisms underlying the normalization of these metrics after successful treatment? Some studies documenting regional atrophy in chronic pain patients sometimes invoke cell death as a mechanism (suggesting that some neurons may die, e.g., in response to excitotoxicity induced by excessive neuronal firing in regions involved in the processing or modulation of nociceptive activity). However, the reversibility of some of these effects within a time frame of mere months, as documented in this and other studies, speaks against this interpretation, given that neurogenesis—while more widespread than initially thought—is very limited in the adult mammalian central nervous system. The structural brain alterations observed in chronic pain conditions may rather reflect changes in dendritic arborization, proliferation or migration of glial cells, or other mechanisms that are more subject to short-term modification than the number of neurons in a given brain region. Ultimately, a well-controlled longitudinal animal study may be necessary to answer these questions.

In addition, further human studies with larger sample sizes will be necessary to determine 1) whether the differences between patients and controls (as well as the changes following treatment) are specifically attributable to pain or also to other factors that differentiate KOA patients from controls and that can potentially change after surgery (e.g., body mass index, physical activity levels, medication usage, insomnia, etc.), 2) whether the observed changes occur in both the roughly 80% of patients with substantive improvement in pain and the 20% whose knee pain does not resolve following TKA, and 3) the nature of the relationship between changes in pain-related variables (e.g., daily pain intensity, temporal summation of pain) and structural changes in the CNS over the course of surgical treatment of KOA.

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