Title: Evidence for central pain mechanisms in chronic post-stroke shoulder pain.

Traditionally, post-stroke shoulder pain (PSSP) is regarded as a peripheral, nociceptive pain. However, treatment is often unsatisfactory and many stroke patients report persistent PSSP. In addition to the biomechanical explanation of PSSP, both the stroke lesion as well as neuroplasticity may alter the function of the pain system and may act as central contributors to the development and maintenance of persistent PSSP. The objective of this study was to assess peripheral and central pain mechanisms associated with persistent PSSP. Somatosensory and supra-spinal endogenous inhibitory functions were assessed in stroke patients with persistent PSSP (n=19), pain-free stroke patients (PF, n=29) and healthy controls (HC, n=23), using clinical examination and quantitative sensory testing combined with a cold pressor test. Sensory abnormalities were more frequently observed and more severe in patients with PSSP, including spinothalamocortical tract (STT) lesions, a feature commonly associated with neuropathic pain. Moreover, signs of central sensitization, such as allostynia at the affected side and generalized hyperalgesia at the unaffected side, were more frequently observed in the patients with PSSP. Supra-spinal inhibitory function was similar in stroke patients and healthy controls. PSSP was not related to the severity of paresis, glenohumeral subluxation or spasticity. This study implies that sensory loss, in particular of the STT, and central sensitization play a role in PSSP that is larger than traditionally assumed. Prevention and treatment might be improved by recognizing both peripheral and central causes of PSSP. Future research should further establish the role of central mechanisms in the development of persistent PSSP.