Short Communication

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Lessons learned – Moving on from QST sensory profiles

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Abstract: Quantitative sensory testing (QST) has been optimized to diagnose in particular small fiber neuropathy and has been successfully used for decades. “Sensory phenotypes” have been derived from the QST data in an attempt to stratify patients with chronic pain and to gain mechanistic insights. However, studies consistently show that there is no difference in sensory phenotypes between neuropathy patients with and without pain and no successful stratification has been shown using the current version of “sensory phenotypes”. Thus, after falsification of the initial hypothesis it is time to focus on more promising approaches.

Keywords: evoked pain; neuropathy; pain mechanism; quantitative sensory testing; stratification.

After decades of pain research, we are still searching for approaches that can stratify patients according to mechanistic factors and potentially to the most promising therapeutic scheme. Individual sensory profiles have been suggested for this purpose hypothesizing that the mechanisms that drive chronic pain also imprint certain patterns in the acutely evoked processing of sensory information. When compared to healthy volunteers, patients with neuropathic pain could be clearly differentiated [1]. However, sensory profiles failed in the crucial test, i.e., separating patients with painful and painless neuropathy [2–5]. Thus, there is a clear consensus that sensory profiles cannot be linked to ongoing pain [5]. Moreover, the predictive value of QST profiles has been falsified in a prospective study of carpal tunnel syndrome [6] “Baseline sensory phenotype category was not associated with surgical outcome” corroborated by a second study [7].

Methodological limitations

When sensory thresholds are assessed, the functionally competent “healthy” nerve fibers are tested, in particular those that innervate the most superficial epidermis. In contrast, spontaneously active nociceptors underlying non-evoked pain are more probable to be “non-healthy” and therefore are less superficial and may not be reached by the stimulus at all.

For determining the “phenotype”, many parameters unrelated to pain (cold, warm, touch, vibration) are assessed at high resolution whereas parameters highly important for pain (punctate hyperalgesia, static allodynia, touch-evoked allodynia) are not quantified at all or only in a course fashion (touch-evoked allodynia). This is not an ideal situation for a composite score focusing on pain.

The large thermode areas (about 10 sqcm) are optimized to detect loss of function for the diagnosis of small fiber neuropathy rather than to detect sensitization and do not allow to adequately assess spatially inhomogeneous sensory changes. Moreover, the flat surface probe on the pressure algometer is inadequate to test deep pain instead spherical tips are to be used to avoid skin distension.

Conceptual flaws

Genuine spatial ambiguity

When chronic pain develops after a peripheral nerve injury such as post thoracotomy, patients often present a skin area of denervation surrounded by an area of hyperalgesia. QST profiles would ideally reflect this as “loss of function” and “mechanical hyperalgesia” phenotype given that contingent homogenous skin areas exist and that two sites in symptomatic skin were tested. However, the QST protocol only picks one test site thereby creating a dilemma. The spatial ambiguity may also explain why the QST protocol has a detection rate for touch-evoked allodynia of only 50% as compared to bedside test [8]. Moreover, considering the large contact areas of the thermodes of about 10 sqcm

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and the pronounced inhomogeneity of skin innervation in neuropathy it is unclear to which extent QST can really spatially resolve particular sensory changes.

Genuine disconnect between sensory phenotype and pain mechanism

Linking a certain sensory phenotype to a specific pain mechanism is a major fundamental flaw of the QST approach. When following up on the above hypothetical patient with traumatic neuropathic pain and a central area of sensory loss the disconnect becomes evident: the sensory loss is based on proximal axotomy that on one hand causes the sensory phenotype of sensory loss; on the other hand, it leaves the local regenerating nociceptors hypersensitive to mechanical and heat stimuli [9] (and spontaneously active [10]). Clinically, the intense and lasting pain that is caused by inadvertent pressure on the neuroma clearly reflects the relevance of such hypersensitivity for the patient. Thus, one mechanism of pain in this “sensory loss” phenotype patient is mechanical hypersensitivity clearly invalidating the claim of mechanistic implications of the “sensory loss” phenotype.

On the other hand, the secondary mechanical hyperalgesia surrounding the anaesthetic spot would be reflected in a “mechanical hyperalgesia” phenotype. However, the ongoing nociceptor activity that is maintaining this secondary mechanical hyperalgesia (and the ongoing pain) can also arise from the cut afferents linked to the “sensory loss” phenotype. Thus, pain mechanisms (mechanical, heat sensitization of cut afferents or non-injured bystanders, spontaneous activity in sensory endings, regenerating sprouts or dorsal root ganglion neurons, spinal sensitization) cannot be linked to the cutaneous sensory profiles (skin hyper/hypersensitivity). Specifically, a “sensory loss” phenotype after nerve lesion definitively is mechanistically linked to mechanical and heat sensitization of the regenerating sprouts, spontaneous nociceptor activity and spinal sensitization.

Study results

There is only one study that has reported a predictive value of QST profiles for pain therapy [11] – however, this predictive value was no longer significant when the current classifications of sensory phenotypes was applied [12]. Notably, the patients with “irritable nociceptor” phenotype also had significantly higher success rate of drug treatment in their history and their quality of life paradoxically decreased significantly as compared to the other phenotypes [11]. Successful sensory profiling (post-hoc) was reported using intact warm and cold thresholds (TRPA1 antagonist study) [13] or intensity of touch evoked allodynia (botulinum toxin study) [14]. Thus, there is not a single study in which the current sensory phenotypes predicted successful pain therapy. Considering these bleak results, it remains unclear why both FDA and EMA still recommend sensory profiles for stratification in pain studies.

Perspective

Quantitative sensory testing has been optimized to detect small fiber neuropathy and has proven efficient and sensitive for that purpose. In contrast, “sensory profiles” derived from sensory testing have multiple technical limitations and suffer from fundamental conceptual flaws. Thus, it is not surprising that “sensory profiles” have proven unsuccessful to differentiate painful from painless neuropathy, are not linked to non-evoked pain and were unsuccessful in stratification of pain patients.

Progress in science is based on falsification of hypotheses thereby continuously adapting and improving our models and approaches. Given the overwhelming evidence against a role of sensory profiles for a better mechanistic understanding of chronic pain or for stratification it is time to accept this failure and focus research resources on alternative approaches.

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References


