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BIOLOGICAL FEATURES

Diagnosis of Altered Central Pain Processing

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Study Design. Nonsystematic review.

Objective. To review the current knowledge on detecting altered central pain processing in individual patients with chronic pain.

Summary of Background Data. Alterations in central pain processing are mainly characterized by hyperexcitability of the central nervous system and disturbances in endogenous pain modulation. Although these mechanisms are widely recognized as important determinants of pain and disability, there is need for translation of this knowledge into benefits for patients. To this purpose, the first step is the detection of abnormalities in pain processing in individual patients. Quantitative sensory tests (QST) explore aspects of nociception and pain perception, and are therefore potentially useful for diagnostic purposes.

Methods. Nonsystematic review of the reliability, validity and reference values of QST for the assessment of altered central pain processing in chronic pain patients.

Results. The reliability of QST is generally high. However, most studies have been performed on healthy volunteers, and few reliability data in patients are available. Furthermore, little is known on the reliability of measures of endogenous pain modulation. The face validity of QST is acceptable. The construct validity cannot be tested, because there is no gold standard for the detection of altered central pain processing in humans. Reference values of different types of QST for applications in neuropathic and musculoskeletal pain have been determined in large samples of pain-free subjects.

Conclusion. QST can be used in clinical practice to assess the presence of sensory abnormalities in individual patients. Because information on the reliability and validity of the tests is incomplete, the findings should be interpreted with caution. It is still unclear to what extent disturbances in central pain processing are relevant for the determination of symptoms in individual patients. Furthermore, the therapeutic consequences of these assessments remain undetermined. These are challenges of future translational research.

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Chronic pain states are characterized by changes in the central processing of sensory input. In line with extensive animal research,[1] it is largely recognized that patients can develop a state of hyperexcitability of the central nervous system and alterations in the endogenous pain modulation.[2] Such changes can result in pain after innocuous sensory stimuli, exaggerated pain sensation after moderately painful stimuli and enlargement of the referred pain areas.[3] All these manifestations are likely to have clinical relevance. For instance, they can be determinants of exaggerated pain with physical activities, which is a major cause of disability.

In the recent years, research has focused on describing these central changes in chronic pain patients. Groups of patients have been compared with groups of healthy volunteers. This almost consistently resulted in differences between patients and controls in the way the sensory information is processed and pain is perceived.[2] However, a close analysis of the data reveals that, whereas statistical differences are frequently detected, data from patients and controls overlap. This implies that stating that patients have central hypersensitivity is basically wrong. Indeed, the difference exists in statistical terms between groups of patients and groups of control subjects. This by far does not necessarily mean that every patient displays central hypersensitivity.

These reflections show that research in the field of pathophysiology has not yet provided an essential tool: the detection of abnormalities in pain processing in individual patients. Until research makes this step, translation of basic knowledge into benefits for patients will be difficult.

This paper focuses on the perspective of detecting abnormal pain processing in individual patients. The rationale behind the use of quantitative sensory tests (QST), the current evidence of validity of these methods and the possible clinical implications are discussed.

ASSESSMENT METHODS

In humans, direct neural recordings relevant for central pain processing cannot be made. QST were developed to assess the responses to sensory stimuli for research purposes.[4] More than two decades of intensive use of QST in pain research have brought an enormous development in this field. Meanwhile, these methods have found their way to clinical practice, particularly in the frame of neuropathic pain. The clinical

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applications are progressively expanding and QST have the potential to provide important information on the nociceptive system of patients with different chronic pain states.

QST has been used extensively in pain research to study central hypersensitivity. The rationale behind this practice is that pain hypersensitivity detected after stimulation of a healthy tissue must be the result of an alteration in the central processing of the stimulus applied. For instance, if patients with neck pain display pain hypersensitivity after the application of a stimulus to the lower extremity, there is no rationale for interpreting this observation as the consequence of a peripheral pathology.[5,6] If detected, such pain hypersensitivity must be the result of central phenomena.

An additional important application is the assessment of endogenous pain modulation by diffuse noxious inhibitory control (DNIC). Under normal conditions, pain after application of a test nociceptive stimulus is attenuated by the application of an additional tonic conditioning stimulus to a remote body region, reflecting diffuse endogenous inhibition.[7]

A critical limitation applies to the use of QST in humans. Although these methods have the potential to provide information on possible abnormalities of the nociceptive system, they cannot tell us what structures are the sites of the alteration and what mechanisms lie behind it. They cannot even tell us whether the increased pain perception is the result of changes in neural excitability and/or stems from exaggerated pain perception at higher brain centers.

Studies using nociceptive withdrawal reflexes have revealed that at least part of the hypersensitivity is the result of spinal hyperexcitability.[8–10] Investigations using brain images have shown that activation of brain areas is enhanced in chronic pain patients who display pain hypersensitivity.[11] Accordingly, brain areas involved in DNIC have been identified.[12] These data indicate that central hypersensitivity has measurable correlates in the central nervous system and is not merely the result of hysteria. Nevertheless, the mechanisms underlying such alterations in central pain processes are probably different in different patients and remain largely obscure in clinical practice.

DIAGNOSIS: REQUIREMENTS AND CURRENT EVIDENCE

If central hypersensitivity and altered endogenous pain modulation are relevant determinants of chronic pain states, detecting them in individual patients is an essential translational step toward clinical applications. This brings us to the field of diagnosis, which, when applied to pathophysiological mechanisms, is a new area of pain medicine.

For a test to be diagnostic, a number of conditions must be met. First, the test must be reliable. Reliability is the degree to which a test measures the same way each time it is used under the same condition with the same subjects. A test that leads to different conclusions, when performed on the same patients by different investigators or at different time points, cannot have any clinical application. Some research on the reliability of QST has been performed. It seems that measurements of pressure, heat, electrical pain and nociceptive reflex have acceptable to good reliability.[13–17] The author is not aware of reliability data on DNIC measurements. It is important to consider that most reliability studies have been conducted on healthy volunteers. It is possible that responses from pain patients would display higher instability, which may impair reliability. Recent data indicate that the reliability of pain and reflex thresholds after electrical stimulation is good also in patients with chronic low back pain, with intraclass correlation coefficients above 0.75.[18] Future research on reliability of QST should be possibly performed on patients, to assess their applicability for clinical practice.

Face validity is the extent to which the test seems "on its face" to sample what we intended it to measure. Most of the measures of altered pain processing have face validity. For instance, the aforementioned assessment of pain sensitivity at healthy tissues is "on its face" a measure of central processing of sensory stimuli, for pathology at the tested tissue is ruled out. Accordingly, the assessment of the latency of nociceptive reflex establishes the face validity of this method as a measurement of spinal cord excitability, because a voluntary muscle contraction can be ruled out by setting temporal limits for the definition of the reflex. However, this does not rule out the influence of descending modulation on spinal nociception. Indeed, additional heterotopic stimulation or experimental emotional conditionings modulate the nociceptive reflex.[19,20]

A further step in the definition of validity of a diagnostic test is the analysis of its construct validity. This can be defined as the extent to which the test is measuring the construct it claims to be measuring. To study construct validity, the test under investigation needs to be compared to a gold standard with an established validity. This would allow the calculation of sensitivity, specificity, likelihood ratios and further parameters that are relevant to define the construct validity of the test. Unfortunately, such gold standards are not available for measurements of altered central pain processing in humans. For instance, studying the construct validity of pressure pain threshold as a measurement of central hypersensitivity would require the assessment of neuronal sensitivity in each tested patient as the gold standard. Such an assessment is unavailable. As a result, the construct validity of measurements of central pain processes remains uncertain.

An essential requirement for an individual assessment of altered pain processing is the availability of reference values in the normal population. This implies the investigation of large samples of individuals and the coanalysis of factors that may interfere with the sensory assessments. Reference values for QST that are suitable for the assessment of neuropathic pain have been defined in 180 healthy subjects.[21] Investigations of 300 pain-free subjects have allowed the definition of reference values for nociceptive reflex paradigms and QST methods that can be applied to musculoskeletal pain states.[22,23] Some, but not all of these assessments are gender dependent. For instance, electrical pain thresholds were not affected by gender.[22] For heat and pressure pain thresholds, gender had a influence only for young ages, whereas for elderly subjects no significant impact of gender was detected.[23] Other parameters, including psychological factors, were found to have either no or a quantitatively small influence on QST. This does not

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support the view that increased pain sensitivity is mainly the result of psychosocial factors.

In summary, reliability of different types of QST is well established for healthy volunteers, but the results need to be replicated in patients with chronic pain. The face validity of measures of central hypersensitivity and altered endogenous modulation is acceptable, but the construct validity cannot be evaluated because of lack of gold standards in humans. Reference values of different QST have been determined in large investigations. Thus, several progresses in the field of clinical applicability of QST have been made. Indeed, these methods are already used clinically in different pain units. However, because of the different limitations inherent in the methods and the gaps in knowledge on their validity, clinicians still need to be careful in the interpretation of the findings.

CLINICAL RELEVANCE

Chronic pain conditions are frequently characterized by a discrepancy between objective signs of tissue damage and magnitude of pain and disability. Extensive research has tried to explain such a discrepancy by psychosocial factors. Although psychosocial factors are largely recognized as important factors in chronic pain, there is no evidence that they explain entirely or to a considerable magnitude the lack of correlation between lesion and complaints. This means that there is still a large gap in our knowledge that needs to be covered by further research.

Altered central pain processing is one of the research areas that may explain part of the complex phenomenology of chronic pain. Indeed, exaggerated central excitability or disturbances in endogenous pain modulation may lead to substantial suffering and disability in the presence of a low-intensity nociceptive stimulus. Theoretically, even innocuous stimulation, such as activation of muscles or load of undamaged joints, may lead to pain sensations when the processing of sensory stimuli is altered. In this way, disturbances in central pain processes have a potential clinical significance.

Despite the large body of evidence behind the concept of altered pain processing, mostly coming from basic research, its clinical relevance is still based on assumptions. These assumptions can be summarized as follows: (1) altered central pain processing is relevant in the determination of symptoms; (2) altered central pain processing can be detected and quantified in individual patients; and (3) treating such disturbances is expected to lead to an improved outcome.

Clinical research has just started addressing the questions behind these assumptions. An area where some progresses have been made is the detection of central hypersensitivity in individual patients (see Section "Diagnosis: Requirements and Current Evidence"). In terms of patient's care, a benefit of such an individual assessment is providing a model to explain patient's symptoms. Indeed, receiving an explanation for their pain is a major expectation for patients attending a pain clinic.[24] Such an assessment is particularly important for patients in which the magnitude of objective signs of tissue pathology does not match the magnitude of the complaints.

An additional important potential application is prognosis. Some initial data indicate that alterations in central pain processing may represent negative prognostic factors. In investigations on whiplash injury, the development of generalized sensory hypersensitivity was related with persistence of pain months after the trauma.[6,25] There is some evidence that central hypersensitivity in whiplash patients represents a negative factor for the efficacy of rehabilitation programmes.[26] Alterations in endogenous pain modulation before thoracotomy was a predictor of chronic pain.[27] Clearly, further studies have to be done to establish and quantify the prognostic value of measures of central pain processing. If such studies will allow the reliable identification of patients at risk, interventions aiming at correcting such alterations could be developed.

Finally, the detection of individual disturbances in central pain processing may allow the development of mechanism-based therapeutic interventions that would specifically target the underlying pathophysiology. To date, research is still far away from providing an evidence-based mechanism-based therapeutic approach.

It is important to stress that the presence of alterations in central pain processes does not rule out the importance of tissue damage as determinant of the symptoms. Correlations between magnitude of nociceptive input and magnitude of central hypersensitivity have been detected in patients with neck and low back pain, suggesting that central hypersensitivity may be driven, at least partially, by a peripheral nociceptive focus.[28,29] In the field of whiplash injury, there is clear evidence that the zygapophysial joints are a source of pain in 30% to 60% of patients.[30,31] At least in some of these patients, central hypersensitivity is expected to amplify symptoms. However, anesthetizing the joints by selective nerve blocks can lead to attenuation of central hypersensitivity.[32] This again suggests that central changes depend on the presence of a nociceptive input.

Denervation of the zygapophysial joints produces complete pain relief in over 70% of patients, if these patients are selected with controlled nerve blocks.[33–35] Assuming that at least part of these patients displayed central hypersensitivity, then its clinical relevance would probably vanish after successful denervation. Additional support for such a dependency of altered pain processing from the peripheral lesion comes from an investigation in hip pain, whereby disturbances in pain perception where reverted after successful hip joint replacement.[36]

On the basis of the above considerations, two essential questions arise: (1) is the clinical relevance of altered pain processes limited to those cases in which no treatment of the peripheral lesion is available? (2) Can such central changes persist after resolution of an initial tissue damage thereby determining the persistence of symptoms? We simply have no human data to give a clear answer to these questions. In the mean time, caution applies to the concept of altered central pain processing as an autonomous disease that is uncoupled from a peripheral lesion, until corresponding evidence is provided.

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CONCLUSIONS

There is clear evidence that groups of patients with different chronic pain conditions display on average altered central pain processing. The main manifestations of this phenomenon are an exaggerated pain perception after low-input stimulation and an enlargement of the pain areas. These phenomena are likely to be clinically relevant in terms of magnitude of pain and disability. However, translation of this concept into clinical benefits requires further research. The clinical relevance is assumed, but not clearly demonstrated. Specific treatments with high efficacy are not available. The dependency of altered pain processing from the peripheral lesion in patients is only partially understood. Accordingly, the presence of such central disturbances does not rule out the importance of peripheral lesions in the determination of the symptoms, even if such lesions are not detectable.

A first translational step in the field of altered central pain processing implies the definition of diagnostic criteria for detecting such alterations in individual patients. Recent research has provided tools for an application of sensory tests for diagnostic purposes. Future perspectives include the development of treatments that are tailored to the individual disturbances in central pain processes.

➢ Key Points

- ❑ Alterations in the central processing of nociceptive input cause pain hypersensitivity in chronic pain patients, which is likely to be an important contributor of pain and disability.
- ❑ Quantitative sensory tests (QST) explore central excitability in humans and have therefore potential usefulness to detect altered central pain processing in individual patients.
- ❑ Reference values for several types of QST are available, data on reliability are encouraging and the face validity is acceptable.
- ❑ Quantification of the role of disturbances in central pain processing for the determination of symptoms in individual patients, as well as the development of targeted treatment modalities, are challenges of future translational research.

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