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Psychological Screening/Phenotyping as Predictors for Spinal Cord Stimulation

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Abstract

Spinal Cord Stimulation (SCS) is becoming a widely used treatment for a number of pain conditions, and it is frequently considered as a pain management option when conservative or less invasive techniques have proven ineffective. Potential indications for SCS include: complex regional pain syndrome (CRPS), postherpetic neuralgia, traumatic nerve injury, failed back surgery syndrome, refractory angina pectoris, peripheral vascular disease, neuropathic pain, and visceral pain [1]. While research on SCS is in its infancy, it is clear that substantial variation exists in the degree of benefit obtained from SCS, and the procedure does not come without risks; thus focused patient selection is becoming very important. Psychological characteristics play an important role in shaping individual differences in the pain experience and may influence responses to SCS, as well as a variety of other pain treatments [2]. In addition to psychological assessment, quantitative sensory testing (QST) procedures offer another valuable resource in forecasting who may benefit most from SCS and may also shed light on mechanisms underlying the individual characteristics promoting the effectiveness of such procedures [3]. Here, we present a brief overview of recent studies examining these factors in their relationship with SCS outcomes.

Keywords

Spinal Cord Stimulation; psychological assessment; QST; pain testing

Introduction

Spinal cord stimulation (SCS) with implantable or externalized systems has been available since the 1960's [4]. The theoretical basis of the efficacy of SCS is based on Melzack and Wall's Gate Control Theory [5] that proposes that stimulation of large nerve fibers overrides the transmission of small nerve fibers that transmit pain. SCS is expected to reduce pain by blocking the conduction of primary nerve pathways [6]. Spinal cord stimulators have reported success rates ranging from 20-70% [7]. Recent reviews have noted the rapid increase in the number of implanted spinal cord stimulators, with annual estimates in the 10,000-20,000 range [8], and some econometric analyses have indicated that SCS may be a

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cost-effective treatment option, particularly for patients with persistent neuropathic pain syndromes [9].

Although outcome studies have reported that SCS is effective in treating chronic pain, there is no clear algorithm for selecting SCS as an optimal treatment choice. Typically, decisions regarding implantation are based on the results of a brief stimulator trial, combined with the clinical judgments of healthcare providers. Original recommendations for SCS patient selection included some psychological criteria such as emotional stability and the absence of depression [2]; indeed, psychological evaluation is often a mandatory part of the pre-screening process prior to consideration for implantable pain-management devices. Collectively, psychological and social issues are common among pain patients. Psychological assessment is designed to identify problematic emotional reactions, maladaptive thinking and behavior, and social problems that contribute to pain and disability. When psychosocial issues are identified, treatment can be tailored to address these challenges, thereby improving the likelihood and speed of recovery and prevention of ongoing or more severe problems. Psychological evaluations typically include the assessment of sensory, affective, cognitive, and behavioral components of the pain experience, expectations of benefit of an implanted device, and identification of personality and psychosocial factors that can influence treatment outcome [10]. The sensory experience is usually best understood through description of the severity, location and temporal characteristics of chronic pain.

A number of studies have examined psychological variables associated with response to pain treatment. In general, a handful of risk factors have been identified that correlate with greater risk for unsuccessful outcomes from pain treatment, including pain chronicity and duration, psychological distress, pain-related catastrophizing, a history of abuse or trauma, nicotine use and substance abuse history, poor social support, and significant cognitive deficits [11]. In general, patients with psychiatric comorbidity and high levels of distress, particularly psychopathology/extreme emotionality have poor responses to treatment [12-14]. It is widely recognized that patients with chronic pain frequently report depression, anxiety, irritability, history of physical/sexual abuse, a personal and family history of mood disorder, and other risk factors for deleterious pain-related outcomes [15]. In chronic pain clinic populations, 50% to 80% of patients with chronic pain had signs of psychopathology [16], making this the most prevalent comorbidity in these patients. This underscores the importance of psychological evaluation for those under consideration for SCS therapy.

Quantitative sensory testing (QST), the systematic application of quantifiable pain induction and measurement techniques, is also being increasingly applied to measure individual patient characteristics that might be associated with long-term pain outcomes, particularly persistent postoperative pain [17]. In general, increased sensitivity to painful stimuli (e.g., low pain threshold and tolerance, high ratings of pain intensity in response to application of a standardized stimulus) may be a risk factor for poor outcomes. Individuals differ widely in their sensitivity to noxious stimulation, and laboratory-based administration of standardized stimuli offers a variety of methods for evaluating these individual differences [18]. This inter-individual variability is multifactorial in etiology with contributions from factors affecting pain sensitivity, pharmacogenomics, psychological, and cultural and environmental factors [19]. Individual differences have significant implications for the clinical experience of pain [20] and early identification of individuals with higher risk of treatment failure would result in better treatment efficacy and side effect profile. Measurements of pain threshold and pain tolerance in response to multi-modal stimuli applied to various anatomic sites can be of great value in quantifying these individual differences in pain sensitivity, and evaluating their clinical relevance. Reviews [21,22] have highlighted the potential value of psychophysical pain assessment, and numerous studies over the past 5-10 years have

demonstrated its potential clinical value. In general, results in this area of research suggest that individuals who are most pain-sensitive, or who show the least effective endogenous pain-inhibitory responses, are at the greatest risk for poor long-term pain outcomes. For example, QST studies have reported that greater pretreatment sensitivity to pain predicts worse post-treatment outcomes of multidisciplinary treatment [23,24]. That is, patients who had the lowest pain threshold and tolerance at baseline benefitted the least (in terms of pain reduction and improved function) from multidisciplinary treatment. Several studies have underscored the importance of examining such QST results in relation to spinal cord stimulation, and pain sensitivity in response to controlled stimulation has been proposed as a somewhat "objective" marker that could help to guide the selection of appropriate SCS candidates [3]. To date, however, few studies have been conducted to investigate the relationship between responses to QST and either short- or long-term SCS outcomes. There are reasonable grounds for hypothesizing that patient variability in QST-assessed pain sensitivity could predict treatment response: Chronic pain is a disease of the nervous system that includes reorganization of spinal cord circuitry and supraspinal neural pathways that respond to persistent peripheral input [25]. Dysregulated central pain-inhibitory and facilitatory mechanisms have been implicated in pathophysiologic models of chronic pain [26-28], and QST offers an array of non-invasive and convenient methods for assessing these central pain processing mechanisms. The application of these methods to the study of SCS in chronic pain patients may clarify the possible mechanisms by which this treatment reduces clinical pain and may help identify which patients may be most suitable for SCS. Below, we review the recent literature on the impact of psychological factors and QST in SCS outcomes.

Psychological Factors

In 2009 a systematic review was conducted to examine whether carefully screening patients could predict pain-related and functional outcomes from lumbar surgery or spinal cord stimulation [29]. Of this large synthesis of literature, only four SCS studies met inclusion criteria, highlighting the need for further research in this area. The authors observed a strong association between psychological factors and treatment outcome in 92% of reviewed studies. Pre-surgical psychological factors including somatization, depression, anxiety, and poor coping were most predictive of poor response to both lumbar surgery and spinal cord stimulation. They found that older age and longer pain duration were also predictive of poorer outcome, while pre-treatment physical findings, activity interference, and pain intensity were minimally predictive. Despite a dearth of empirical evidence, the authors conclude that psychological screening before device implantation may be predictive of treatment outcome. Another recent review of psychosocial characteristics as predictors of outcomes following SCS indicates that depression appears to be the psychosocial factor most strongly linked to reduced efficacy of SCS [8]; however, depression and quality of life may also improve following successful SCS [30,31], and future studies would likely benefit from assessing both pre-treatment levels of depression and treatment-associated changes in depression.

Screening and Assessment Components

When patients are determined to be eligible and potential candidates for SCS, a psychological assessment is often requested. Psychological evaluation is designed to help identify an ideal patient to achieve maximum benefit from an implanted device. The evaluation should include valid and reliable assessments of subjective pain intensity, mood and personality, activity interference, pain beliefs and coping. Patients typically undergo a trial of SCS designed to determine its efficacy and aid physicians in clinical decision-making regarding appropriateness for permanent SCS. The trial consists of temporary

placement of a stimulator lead for 4 to 10 days. A successful trial includes self-reported pain reduction by 50% and overall patient satisfaction.

Cognitive, affective, and personality-related variables

Overall, many factors are likely to play a role in shaping pain outcomes following implantation of a pain management device; however, no consensus exists on what factors are the strongest and most consistently predictive of outcomes. Most studies evaluating the impact of psychological/psychosocial influences on SCS outcomes evaluate associations between these variables and short-term SCS effectiveness; long-term follow-up is rare. Burchiel and colleagues [31] found that patient age, depression (measured using the Minnesota Multiphasic Personality Inventory subscale D), and the evaluative subscale of the McGill Pain Questionnaire (MPQe) were important predictors of posttreatment pain status. They noted that increased patient age and depression were associated with higher levels of post-implantation pain intensity (e.g., worse outcomes). However, higher MPQe scores (possibly related to the floor effect) correlated with improved pain status. Using these parameters, they were able to correctly predict success or failure at 3 months in 88% of their study population.

Cognitive capacity may also be an important factor to consider in screening patients for SCS, though empirical studies are few. In a recent review suggesting recommendations for SCS patient selection, Atkinson and colleagues [32] note that cognitively impaired individuals should likely be precluded from SCS treatment unless adequate support is provided by a care team/social services. In addition, they also note that those with unresolved psychological issues including active psychosis, major untreated mood disorders and somatization should not be eligible. Substance use, including alcohol, drugs or medications are also contraindications for positive SCS outcomes. They also reviewed recent literature suggesting the age, duration and location of pain, intensity and presence of mechanical hypoesthesia (reduced sensation, measured through mechanical detection threshold) did not predict SCS success in CRPS patients.

Coping and Beliefs

Pain perception, beliefs about pain, treatment expectations, pain acceptance, and coping mechanisms are widely recognized as important factors for predicting the outcome of treatment, and may be particularly relevant as predictors for implantable devices. Patients with adequate psychological functioning are more likely to ignore their pain, use adaptive coping self-statements, and remain active in order to divert their attention from their pain [33]. Sparkes and colleagues, in a 2012 review of the SCS literature [34], found that coping with pain and emotional impact on coping was a major determinant of SCS outcomes for patients. The authors suggest improved education/preparation and Cognitive Behavioral Therapy (CBT) for patients prior to undergoing SCS, as these approaches may serve to minimize and buffer the effects of negative affect during the treatment period. Others have also noted the importance of combining psychosocial intervention with implantable devices to improve outcomes [35]. In addition, offering SCS candidates the ability to have contact with other patients that had been through the SCS process may help to improve communication, reduce distress, and improve outcomes. Not surprisingly, patients who have unrealistic beliefs and expectations about their condition are also poor candidates for this type of pain treatment. Despite the importance of coping, catastrophizing (a passive dimension of pain coping characterized by magnification of pain-related symptoms, rumination about pain, feelings of helplessness, and pessimism about pain-related outcomes) was found to not predict the efficacy of SCS in pain reduction, global perceived effect of the SCS or quality of life [36]. While this is the only study to date specifically examining pain

catastrophizing in relation to SCS, the results are counterintuitive as catastrophizing is one of the key psychological predictors of successful pain treatment outcomes [37].

Quantitative Sensory Testing (QST)

Quantitative sensory testing (QST), in which standardized noxious stimuli (e.g., thermal cold or heat, mechanical pressure or vibration, electrical testing, etc.) are administered under highly controlled conditions, can reveal the presence of hypersensitivity as well as dysfunction in pain systems. The pain experience is shaped by a complex array of factors. Similar to the inescapability of cognitive, emotional and sociocultural aspects contributing to pain variability, QST responses are influenced by interpersonal variables and may shed light on pain outcomes. The effectiveness of SCS is variable in different chronic pain states and across patients with similar etiologies for their pain. Therefore, a better understanding of the neural circuits that are stimulated and the neurophysiological and biochemical mechanisms underlying the antinociceptive/ antithyperalgesic actions of SCS may help develop strategies to improve the selection criteria and/or efficacy of SCS. Collectively, however, the mechanisms of action for successful SCS remain poorly understood [38]. A few hypothesized mechanisms include a potential gating effect of incoming nociceptive stimuli in the dorsal horn of the spinal cord, and activation of descending pain inhibitory pathways via supraspinal mechanisms [39]. Many non-human animal studies have examined potential mechanisms, though few have been translated to humans. One such study found preliminary evidence for using sensory testing procedures to assist clinicians in selecting patients for permanent stimulation [3]. They found that vibration threshold and electrical tolerance changed with SCS trial (see below) and that these results were significantly associated with the decision to have a permanent SCS.

At present, a number of measures exist to evaluate pain responses. Traditional measures, including pain thresholds, tolerance and supra-threshold stimuli are ‘static’ measures which depict a single point on the pain experience continuum. Though useful, recent evidence suggests they may be less likely to fully capture the endogenous pain modulatory processes that occur postoperatively [17]. ‘Dynamic’ QST measures involving multiple or repetitive stimuli may have stronger clinical relevance and/or predictive ability [40], though little work has been conducted in SCS using dynamic measures.

Static Measures

Thresholds

Several studies have examined detection threshold (first noticeable sensation), pain threshold (first experience the sensation as painful) and/or tolerance (when no longer able to withstand the sensation) to heat, cold or vibratory stimuli. An early study by Lindblom and Meyerson [41] found elevations in tactile and vibratory thresholds during dorsal column stimulation. Eisenberg and colleagues [3] also found that vibration threshold changed with SCS trial and that these alterations corresponded with patient’s decision to have a permanent SCS. Marchand and colleagues [42] found heat discrimination and pain threshold changes with dorsal column stimulation when compared with placebo stimulation. Vibration threshold and tolerance to electrical stimulation has also been reported to change during SCS trial and these alterations were associated with the decision whether or not to have a permanent implant [3]. However, others have noted no change in thermal thresholds [3,43]. Interestingly, Kemler and colleagues [43], found initial increases in pressure pain threshold among SCS patients; these thresholds had returned to normal three months later, suggesting that the time frame of testing is likely an important factor. Another study assessed static QST responses both during active SCS and with the device turned off; they found significantly delayed cold, warmth and touch detection thresholds within the affected side

when compared to the contralateral unaffected side without stimulation [44]. Not surprisingly, significantly greater mechanical pain thresholds were observed on the unaffected side when compared to the affected side. During active SCS all thermal and vibration thresholds were in the normal range and no differences were observed between the affected and unaffected sides. Mechanical detection threshold, however, remained significantly lower on the affected side. There were also significant differences between cold, warmth and mechanical detection thresholds on the affected side when comparing active and inactive SCS. These results suggest that some physiological parameters may return to normal processing during stimulation. Unfortunately, these studies did not seek to differentiate individuals successfully completing a trial SCS series and those that were unsuccessful.

Allodynia/Hyperalgesia

Allodynia, feeling pain to a normally nonpainful stimulus, and hyperalgesia, an increased response to a painful sensation, are also frequently measured as part of a complete QST paradigm depending on the specific population. Complex regional pain syndrome (CRPS), for example, is characterized by allodynia and hyperalgesia and SCS is frequently used in this population. Kemler and colleagues [43], in one of the few long-term SCS studies, found that dynamic (brush evoked) and static (gentle force, gradual pressure) mechanical hyperalgesia were reduced with SCS and this was sustained over 12 months in CRPS patients. However, Van Eijs and colleagues [22] found brush evoked allodynia to be a significant negative prognostic factor of SCS treatment outcomes after one year in chronic CRPS patients. It is unclear how to resolve this discrepancy, though the severity of the allodynia may be a factor. Williams and colleagues suggested this notion and recently found that the presence of allodynia and/or hyperalgesia was associated with a positive SCS trial and long-term outcomes [23].

Dynamic Testing

Electrical Testing

In contrast to the QST methods described above, which rely on patient report of subjective sensations, some electrical stimulation paradigms have the capacity to assess involuntary sensorimotor reflexes mediated by large and small diameter sensory afferents. In a study of 20 failed back surgery syndrome patients, de Andrade and colleagues [22] found significant alterations in the h-reflex (assessment of modulation of monosynaptic reflex activity in the spinal cord) and nociceptive flexion reflex (NFR; polysynaptic spinal withdrawal reflex) thresholds. The authors noted “strong objective evidence of a real analgesic efficacy of the procedure” based on the change in NFR. These findings may suggest changes in CNS-pain modulatory mechanisms, and show that SCS is able to inhibit activity in both nociceptive (R3-reflex) and non-nociceptive (H-reflex) myelinated sensory afferents at segmental spinal or supraspinal levels. Complex modulating effects can be produced by SCS on various neural circuits, including a broad inhibition of both noxious and innocuous sensory information processing. Eisenberg and colleagues [3] also found that tolerance to electrical stimulation at 5 and 250 Hz was altered during SCS trial, which was associated with decisions of whether or not to have a permanent SCS. Polacek and colleagues [23] used evoked potentials to study EEG response during SCS using similar electrical stimulation and found significant differences (comparing stimulation during active SCS to the same stimulation without active SCS) in evoked potentials in multiple pain-processing brain regions. They concluded that altered cortical somatosensory processing may reduce allodynia. Another electrical processing study examined the value of measuring preoperative central conduction time (CCT) of somatosensory evoked potentials (SSEPs) as a potential predictor of outcomes following SCS [45]. They found that pathological CCT was

significantly associated with low SCS effectiveness. Impressively, none of the patients with significantly abnormal CCT had successful SCS stimulation, while over 75% of those with normal SSEPs were successful.

Temporal Summation

Temporal summation of pain – an index of central pain processing and a human QST-based analogue of "wind-up" – is thought to be mediated by NMDA receptor activity at C-fiber dorsal horn sensory neurons [46]. The testing assesses the enhancement of pain caused by repeated noxious stimulation; animal studies have shown that it involves sensitization of 2nd-order dorsal horn neurons in the spinal cord [46-48]. In humans, temporal summation is thought to reflect endogenous pain-modulatory processes arising from supraspinal structures [48] and it has also been implicated in pathophysiologic models of chronic pain [49], with several conditions such as fibromyalgia [50,51] and TMD [52,53] characterized by pathologically enhanced temporal summation. Preliminary data from our group indicates that SCS produces a significant reduction in temporal summation of pain [54], which hints at the possibility that SCS may alter central pain processing mechanisms in general, and NMDA circuitry in particular [46]. In addition, these pathways, especially as related to NMDA neurotransmission, may be connected to, and have a complex reciprocal relationship with, psychological factors [55].

Imaging Studies

Several functional neuroimaging studies have recently been conducted to identify the effects of SCS on brain responses to pain. Stancak and colleagues [23] tested eight FBSS patients to assess brain regions affected by SCS and experimental heat pain. During SCS, an increase in activity in the primary motor cortex (foot/perineal regions), somatosensory cortex, and insula were observed, with simultaneous decreases in activity in the hand/elbow/shoulder regions of the primary motor cortex. Applying a standardized suprathreshold heat stimulus to the lower leg of study subjects produced increases in the secondary somatosensory cortex, insula, thalamus and cingulate cortex. During simultaneous spinal cord and painful heat stimulations, the left and right temporal poles and the ipsilateral cerebellar cortex were activated more strongly compared to the sum of the activations of the separate stimulations, suggesting modulation of pain-related activation by ongoing spinal cord stimulation. Nihashi and colleagues [56] conducted FDG (fluorodeoxyglucose) PET scanning to provide metabolic/glucose uptake information in seven CRPS patients and 13 controls. They found an increase of FDG metabolism in the left thalamus, secondary somatosensory cortex, anterior cingulate cortex, bilateral insula, dorsolateral prefrontal cortex and bilateral superior temporal gyrus in the six patients where SCS was effective (defined by greater than 50% pain reduction). However, FDG uptake decreased in the posterior cingulate cortex (PCC), right temporal tip, amygdala, primary motor cortex (MI), medial prefrontal cortex (MPFC) and secondary somatosensory area. Alternate findings were observed for the one participant without an effective SCS response. The authors concluded that thalamic activation might be related to whether or not SCS is effective. In a study of SCS and neuropathic pain, Kishima and colleagues [57] conducted PET scanning prior to SCS and at six months to one year post implantation in nine neuropathic pain patients. Pain intensity was reduced by SCS, and the authors also reported significant regional cerebral blood flow (rCBF, $H_2\ ^{15}O$) increases following SCS in the thalamus, orbitofrontal, parietal, anterior cingulate cortex, and prefrontal cortex. Blood flow increases in the dorsolateral prefrontal cortex and related prefrontal areas were correlated with pain reduction in these patients (i.e., individuals with larger PET-assessed increases in rCBF after SCS reported relatively larger decreases in clinical pain intensity following SCS), suggesting that increasing or normalizing neural activation in these areas might serve as a mechanism by which SCS improves pain.

Conclusions

Identifying objective assessments that could aid in the selection of appropriate candidates for an SCS trial would be immensely helpful in patient selection and would spare those who are not the best candidates from this rather invasive procedure. Recommendations for SCS patient selection have always included psychological evaluation [2], though no consensus to date has been reached regarding what specifically the assessment should include and what cut-off levels should be adopted for various questionnaire measures. Future studies should continue to examine psychological characteristics that influence the appropriateness for SCS and long-term follow-up of these variables and SCS success. Advances in technology and electronic data capture may be an efficient way of assessing daily fluctuations in pain and psychological variables as well as communicating them with the care team. Pre-SCS assessment and classification of patients may help in identifying individuals who will benefit most from such treatment. Future studies may also examine modifiable risk factors and how treatment may positively impact SCS outcomes. Such research would have profound implications for enhancing SCS treatment, and may extend the benefit of this procedure to challenging “high risk” chronic pain patients.

QST assessment with reliable and valid cut-off values could be extremely valuable in the selection of SCS patients as well. Eisenberg and colleagues [3] proposed two steps required for identifying tests that may be used to help clinicians determine successful trial candidates. They noted that measures should be identified that are altered by the SCS trial and that the association between these alterations and subjective reductions in pain report achieved through the SCS trial should be well established. While several QST measures appear to be responsive to SCS, few studies have specifically focused on the trial period or the relationship with reduction in pain ratings. The recent literature is somewhat mixed on whether or not detection or pain thresholds and/or tolerances vary as a function of SCS and whether these changes are long- lasting. Allodynia may also be an important consideration in potential SCS candidates, and additional research is required to determine whether individual differences in pre-treatment allodynia or SCS-associated changes in allodynia could serve as predictive markers of long-term treatment outcomes. Collectively, recent evidence suggests that dynamic measures may be more useful than static measures in predicting outcomes of relevant interventions [10], and factors such as temporal summation should be included in future QST studies of SCS [54] [17]. Few human studies to date have assessed dynamic quantitative sensory testing measures that are thought to assess the integrity of central pain processing mechanisms and the efficiency of descending systems that may work on the same systems/influence the effects of SCS. Dynamic QST responses, at least those using electrical measures, appear to be altered over time through use of SCS. In addition, several functional neuroimaging studies indicate that SCS has significant effects on blood flow and neural activity in multiple pain-relevant brain regions, producing increases in some and decreases in others. Future work in this area may identify patterns of activation (either at baseline or during an SCS trial) that are associated with the eventual success or failure of SCS as a treatment modality. Currently, while QST techniques are useful in understanding pain processing in SCS patients and neuromodulation/plasticity between patient groups and over time, it is not clear at the present time what role QST will play in patient selection. It may, one day, be a valuable tool in the screening process for enhancing patient selection in those under consideration for SCS trial.

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