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Can Central Sensitization After Injury Persist as an Autonomous Pain Generator? A Comprehensive Search for Evidence

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Abstract

Objective. To conduct a comprehensive search for evidence with regard to whether central sensitization after an injury can act as a persistent autonomous pain generator after the inducing injury has healed. **Methods**. We searched Medline on PubMed and the Cochrane Library, screening 3,572 abstracts, from which 937 full-text articles were obtained, with 186 of these discarded as irrelevant to the question being posed. The remaining 751 articles were studied for evidence. **Results**. Fourteen publications were judged to provide weak evidence for the hypothesis of central sensitization as a persisting autonomous pain generator, but none addressed the question directly. No strong evidence for the affirmative answer was found. Sixty-one publications were judged to provide weak evidence for a negative answer, and ten were judged to provide strong evidence. Unexpectedly, serious weaknesses were discovered in the literature underpinning the validity of the clinical diagnosis of central sensitization in humans: 1) inappropriate extrapolation, in many publications, of laboratory animal data to humans; 2) failure to demonstrate the absence of peripheral pain generators that might be perpetuating central sensitization; and 3) many factors now shown to confound what is being measured by quantitative sensory testing, conditioned pain modulation, and the Central Sensitization Inventory. **Conclusions**. We found no evidence proving that central sensitization can persist as an autonomous pain generator after the initiating injury has healed. Our review has also shown that the evidential basis for the diagnosis of central sensitization in individual patients is seriously in question.

Key Words: Central Sensitization; Chronic Pain; Central Sensitization Diagnosis

Introduction

In the five decades since Melzack and Wall [1] published their revolutionary theory of spinal cord gate control, there have been enormous advances in our understanding of the neurophysiology of pain. Within this sphere, the concept of central sensitization (CS) has changed our perception of chronic pain and provided huge impetus to the investigation of the persisting problem of the failure of drugs and other measures targeting peripheral nociceptors to provide ongoing pain relief in many clinical situations.

The most recent definition of CS by the International Association for the Study of Pain (2019) is "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input" [2]. This is the definition with which we chose to work. Our review specifically does not encompass central pain syndrome stemming from injury to the central nervous system [3].

No matter how the phenomenon might best be defined, the concept appears to have gained almost universal acceptance, and there is now a widely held belief

[4–19] that after a recoverable painful injury (such as lumbar disc prolapse), healing of the painful injury may be followed by indefinite perpetuation of pain, even widespread pain, by virtue of the CS that was a consequence of the original injury.

The consequences of such acceptance could be profound and far-reaching in terms of (mis)directing treatment options in chronic pain management and in the pursuit of compensation claims after seemingly trivial injury. It was for these reasons that a wide literature search was undertaken to examine the evidence for the existence and influence of CS in everyday clinical practice.

The aims of the present study were 1) to conduct a comprehensive search for evidence with regard to whether CS after an injury can act as a persistent autonomous pain generator (PAPG) after the inducing injury has healed, and 2) to undertake an extensive analysis of the factual bases for the diagnosis of CS in humans.

Methods

Peer-reviewed journals were searched by Medline on PubMed and the Cochrane Library. Search terms for Medline were "pain," "central," "sensitization," and combinations thereof, and the search term for the Cochrane Library was the Medical Subject Heading (MeSH) descriptor "Central Nervous System Sensitization." The time period was limited only by the search engines. Therefore, the only necessary inclusion criterion for any article to be studied in detail was the term "sensitization" used in relation to pain. Table 1 outlines search results and sorting numbers.

We identified 3,572 abstracts, obtaining 937 full-text articles. One hundred eighty-six articles were discarded as irrelevant to the search question; hence, we studied the remaining 751 articles for evidence. Table 2 lists the classifications of the final 751 studied publications, plus a selected 17 of the further 30 data points recorded for each article in an individual Filemaker® record (Claris International Inc., Sunnyvale, CA, USA).

Definitions of Evidence Quality by Type of Publication

Referenced Review Publications

Whether referenced review publications were arguing for or against CS having a PAPG role either after injury or in the CS syndromes, they were classified as containing new evidence if either of the following applied:

1. They presented meta-analysis, rather than just a recounting and discussion of previously published evidence.
2. They presented authoritative integration and analysis of previously published evidence, bringing new insights to the field.

Review Publications Containing Multiple Unreferenced Assertions

Review publications containing multiple unreferenced assertions were classified as discussions and not classified as evidence.

Table 1. Sorting of records

Records identified in primary search	6,553
Duplicates and records removed by title screening	3,559
Records remaining from search	2,994
Additional records from cross-referencing	578
Records included in qualitative analysis	3,572
Full text records studied	937
Records excluded as not on topic	186
Final record study	**751**

Publications Presenting New Evidence in Favor of the Hypothesis of CS as a PAPG

Initially, we framed an exacting set of criteria for what we would regard as evidence of at least Class 2 validity in support of the hypothesis—specifically, human laboratory or clinical evidence consistent with the hypothesis of post-injury CS as a PAPG and fulfilling the following three conditions:

1. Diagnosis of CS by Quantitative Sensory Testing (QST), Conditioned Pain Modulation (CPM), or the Central Sensitization Inventory (CSI).
2. Reasonable grounds for assuming no peripheral pain generators perpetuating the CS.
3. Exclusion, or at least consideration of, psychosocial generators of general hypersensitivity, such as primary psychopathology, personal injury claims, or other forms of secondary gain.

However, as our investigation progressed, we found that not a single publication satisfied these strict criteria. Therefore, we significantly relaxed our criteria for evidence in favor of CS acting as a PAPG to include human clinical studies demonstrating any evidence in this regard.

Publications Presenting New Evidence Against the Hypothesis of CS as a PAPG

To be regarded as presenting new evidence against the hypothesis of CS as a PAPG, publications were required to demonstrate one or more of the following:

1. Psychological/psychosocial influences on the results of QST, CPM, or CSI testing, undermining the validity of CS studies that have failed to consider these influences.
2. Persistent peripheral pain generators in clinical diagnostic groups previously hypothesized only to have pain generated by autonomous CS.
3. Reversibility of QST, CPM, or CSI parameters in patients with chronic pain and CS after therapeutic interventions directed at peripheral pain generators.
4. Reversibility of brain functional magnetic resonance imaging (fMRI) changes seen in brains of patients with chronic pain and CS after therapeutic interventions directed at peripheral pain generators.

Results

The final 751 articles were classified as listed in Table 2, with the levels of evidence detailed in Tables 3–5. The

Table 2. Classification of final 751 relevant publications studied in full text, plus a selected 17 of the total 30 data points documented for each publication in its Filemaker® record (Claris International Inc., Cupertino, CA, USA)

(1) Article type:	
(i) Human study	384
(ii) Animal study	74
(iii) Referenced review	137
(iv) Discussion	156
	751
(2) With respect to the question of "Can CS lead to persisting autonomous pain generation (PAPG)?":	
(a) Relevant to the question, but neither positive nor negative evidence	665
(b) Poor-quality evidence in favor of affirmative answer to the question	14
(c) Good-quality evidence in favor of affirmative answer to the question	0
(d) Poor-quality evidence in favor of negative answer to the question	61
(e) Good-quality evidence in favor of negative answer to the question	10
	751
(3) Aspects of CS in situations of acute pain in humans:	
(i) Symptoms	
(ii) Neurotransmitters	
(iii) Quantitative sensory testing	
(iv) Other neurophysiological evidence	
(v) fMRI	
(vi) Other	
(4) Aspects of CS in situations of chronic pain in humans:	
(i) Symptoms	
(ii) Neurotransmitters	
(iii) Quantitative sensory testing	
(iv) Other neurophysiological evidence	
(v) fMRI	
(vi) Other	
(5) With respect to human trials, reviews, or reports of cases/series alleging PAPG:	
(i) Whether in the reported cases there has been search for, or consideration of, any history of symptoms before the index injury or disease process that could have implied a preexistent state of CS.	
(ii) Whether in the reported cases there was adequate validation of the diagnosis of CS by QST, CPM, or the algorithm and criteria of Nijs et al.	
(iii) Whether the injury or disease process that is alleged to have initiated the CS has demonstrably healed or been otherwise neutralized.	
(iv) Whether consideration has been given in the study cohort to other causes of symptom/disability magnification and persistence, including psychological, social, or secondary gain factors.	
(v) Whether the concept of CS as a PAPG after healing of the initiating injury was assumed by the authors to be established fact.	

following is an analysis of evidence in article categories 2(b) through 2(e) in Tables 2 and 3.

Evidence Category 2(b): Analysis of Publications Judged to Provide Weak Evidence Consistent with the Concept of CS as a PAPG (Table 3)

Fourteen publications were judged as providing weak evidence for the affirmative answer to our question.

In the search for publications that we could classify in the "weak positive evidence" group, we were unable to find a single article that bore directly on the question at issue. Accordingly, we tried to be generously inclusive of publications that expanded the field generally, with possible extrapolation to our question. The 14 publications in the weak positive evidence group can be summarized as follows.

Several studies attempted to show that elevated pain sensitivity demonstrated by QST, CPM, or CSI testing predicted ongoing disability from chronic low back pain [20], poorer quality of life after spinal fusion operations [21], nonresponse after physiotherapy for osteoarthritis [22], postoperative pain after knee replacement [23], high pain levels in osteoarthritis patients even with low-grade disease [24], and persistence of whiplash pain after motor vehicle accidents [25]. However, the confounding factor that was rarely addressed in these publications was the assessment of whether occult peripheral pain generators might have been continuing to drive CS.

Similarly, this question of possible persistent occult peripheral pain generators weakened reviews that offered otherwise commendable analysis, such as that of Lee et al. (2011) [26] on chronic pain in fibromyalgia,

Table 3. Evidence categories 2(b) and 2(c): Articles with weak or strong evidence for an affirmative answer to the question "Can CS persist as a PAPG after resolution of the primary pain generator?"

Reference Number	Author Considered?	Review?	New Evidence of CS as PAPG?	fMRI/ MRI Evidence	QST/ CPM Evidence?	CSI Evidence?	Pain Generator Assessed?	Secondary Gain
2(b): Articles with weak evidence for an affirmative answer to the question "Can CS persist as a PAPG after resolution of the primary pain generator?"								
21	Bennett et al., 2017		Y			Y	N	N
27	Cagnie et al., 2014	Y	Y	Y			N	
16	Clark et al., 2017	Y	Y		Y		N	N
29	Deitos et al., 2015		Y				N	
20	Dubois JD et al., 2016		Y		Y		Y	N
24	Finan et al., 2013		Y		Y		N	N
31	Jensen KB et al., 2010		Y	Y	Y		N	
23	Kurien et al., 2018		Y		Y		N	N
7	Latremoliere A et al., 2009	Y	Y					
26	Lee YC et al., 2011	Y	Y				N	
18	McCarberg et al., 2019	Y	Y				N	
22	O'Leary et al., 2018		Y		Y		N	N
25	Sterling et al., 2003		Y		Y		N	N
5	Woolf CJ, 2007.	Y	Y					
2(c): Articles with strong evidence for affirmative answer to the question "Can CS persist as a PAPG after resolution of the primary pain generator ?"								
Nil								

Y indicates type of article and content; N indicates weakness in article.

Table 4. Evidence category 2(e): Articles with strong evidence for a negative answer to the question "Can CS persist as a PAPG after resolution of the primary pain generator?"

Reference Number	Author	Review?	New Evidence Against CS as PAPG?	fMRI/ MRI Evidence	QST/ CPM Evidence?	CSI Evidence?	Pain Generator Assessed?	Secondary Gain Considered?
140	Gwilym SE et al., 2010		Y	Y				
146	Haroutounian S et al., 2014		Y		Y		Y	
144	Meacham K et al., 2017	Y	Y					
39	Muller M et al., 2019		Y		Y		N	
135	Obermann M et al., 2009		Y	Y				
62	Paras ML et al., 2009	Y	Y					
139	Rodriguez-Raecke R et al., 2009		Y	Y				
136	Seminowicz DA et al., 2011		Y	Y				
57	Tesarz J et al., 2016		Y		Y		N	
93	Voorhies RM et al., 2007		Y				N	Y

Y indicates type of article and content; **N** indicates weakness in article.

osteoarthritis, and rheumatoid arthritis, and that of Cagnie et al. (2014) [27] on structural and fMRI findings in fibromyalgia.

There were also highly authoritative reviews of experimental literature, such as those of Woolf (2007) [5] and Latremoliere and Woolf (2009) [7], presenting what was known at those times about the mechanisms of CS with regard to neurophysiology and neurochemistry. Nevertheless, neither of these articles proved CS to be capable of acting as a PAPG after healing of an inducing painful injury in humans.

There have also been speculative discussions, such as those of Mansour et al. (2014) [28] and McCarberg et al. (2019) [18], arguing for permanence of CS to pain due to plastic changes in mesolimbic-prefrontal cortical circuitry, akin to memory.

The only report of a measurable finding in humans with CS was the study of Deitos et al. (2015) [29], who found elevated levels of brain-derived neurotrophic factor, tumor necrosis factor-α, and interleukins 6 and 10 in female patients with CS syndrome absent any structural pathology. There has been criticism of that article [30], and there appear not to have been further publications validating that finding.

Lastly, there have been numerous studies purporting to show significant influence on QST, CPM, and CSI

Table 5. Evidence category 2(d): Articles with weak evidence for a negative answer to the question "Can CS persist as a PAPG after resolution of the primary pain generator?"

Reference Number	Author	Review?	New Evidence Against CS as PAPG?	fMRI/ MRI Evidence	QST/ CPM Evidence?	CSI Evidence?	Pain Generator Assessed?	Secondary Gain Considered?
69	Afari N et al., 2014	Y	Y					
130	Ang DC et al., 2010		Y		Y			
148	Argoff CE, 2018	Y	Y					
100	Arnold et al., 2004		Y		Y			
36	Backonja MM et al., 2013	Y	Y		Y			
51	Chaichana KL et al., 2011		Y				N	
81	Clark JR et al., 2018		Y			Y	N	N
82	Clark JR et al., 2019		Y			Y	N	N
83	Clark JR et al., 2019		Y			Y	N	N
48	Coronado RA et al., 2018		Y		Y	Y	N	N
64	Dannlowski U et al., 2012		Y	Y				
142	De Lange FP et al., 2008		Y	Y				
134	De Oliveira SD et al., 2019	Y	Y					
102	Desmeules J et al., 2014		Y		Y			
44	Edwards RR et al., 2016	Y	Y					
141	Erpelding N et al., 2016		Y	Y				
85	Ferrari R, 2010		Y		Y		N	N
84	France CR et al., 2016		Y		Y			
145	Freeman MD et al., 2009		Y		Y		Y	N
70	George SZ et al., 2009		Y		Y		N	N
47	Gervais-Hupé J et al., 2018		Y		Y	Y	N	N
79	Geva N et al., 2014		Y		Y			
61	Heim C et al., 2009		Y					
35	Hubscher M et al., 2013	Y	Y		Y			
89	Iles RA et al., 2009	Y	Y					
127	Jensen MP et al., 2014	Y	Y					
63	Jones GT, 2016	Y	Y					
104	Kato K et al., 2009		Y					
56	Klyne DM et al., 2019		Y		Y		N	N
91	Koffel E et al., 2016		Y				N	N
133	Krafft S et al., 2017		Y		Y			
74	Kregel J et al., 2018		Y		Y	Y	N	N
40	Leung YY et al., 2019		Y		Y			
11	Lewis JD et al., 2012	Y	Y					
17	Malfliet A et al., 2018		Y	Y	Y	Y	N	N
41	Marcuzzi A et al., 2016	Y	Y		Y			
67	McKernan LC et al., 2019		Y			Y	N	N
38	Mlekusch S et al., 2013		Y		Y		N	N
68	Moeller-Bertram T et al., 2012	Y	Y					
65	Moeller-Bertram T et al., 2014		Y		Y		N	N
54	Moss-Morris R etal, 2011		Y					
87	Nahman-Averbuch et al., 2016		Y		Y			
12	Neblett R etal, 2015		Y			Y	N	N
86	Nir RR et al., 2012		Y		Y			
149	Nystrom NA et al., 2018		Y		Y		N	N
37	O'Leary H et al., 2017	Y	Y		Y			
76	Peters ML et al., 2005		Y				N	N
71	Rivest K et al., 2010		Y		Y		N	N
132	Salomons TV et al., 2014		Y		Y			
137	Seminowicz DA et al., 2013		Y	Y			N	
53	Sinikallio S et al., 2011		Y				N	N
92	Smith MT et al., 2019		Y		Y			
96	Sturgeon JA et al., 2017		Y				N	N
73	Taub CJ et al., 2017		Y		Y		N	N
58	Tesarz J et al., 2015		Y		Y		N	N
49	Van Wilgen CP et al., 2017		Y			Y	N	N

(continued)

Table 5. continued

Reference Number	Author	Review?	New Evidence Against CS as PAPG?	fMRI/ MRI Evidence	QST/ CPM Evidence?	CSI Evidence?	Pain Generator Assessed?	Secondary Gain Considered?
143	Walitt B et al., 2016	Y	Y	Y				
80	Wynne-Jones G et al., 2006		Y				Y	N
131	You DS et al., 2014		Y		Y		N	
15	You DS et al., 2016		Y		Y			
59	You DS et al., 2016		Y		Y			

Y indicates type of article and content; **N** indicates weakness in article.

from psychological and other factors [*vide infra* 2(d) and 2(e)]. The only publications we found presenting evidence to the contrary were those of Jensen et al. (2010) [31] and Dubois et al. (2016) [20]. Jensen et al. (2010) [31] found that negative mood in patients with fibromyalgia can lead to a poor self-perception of health, but this was not correlated with the response to computer-controlled pressure stimulation of the thumb or to fMRI measurement of brain activity. Dubois et al. (2016) [20] conducted a longitudinal study of low back pain patients, and after a hierarchical regression was conducted while controlling for clinical pain at 6 months, found that only CPM was a strong correlate, not QST.

As examples of our adoption of an "over-inclusive" attitude to consider any evidence that might bear on the question at issue, three articles are worthy of mention, insofar as they present significant evidence of persisting pain generation by dorsal root ganglion neurons after peripheral nerve injury. Noordenbos and Wall (1981) [32] reported seven patients with peripheral nerve injuries who were treated unsuccessfully by conservative methods for periods ranging from 3 to 109 months, after which all then had the damaged nerve resected, with sural nerve graft in five cases. Examined 20–72 months after nerve grafting, all seven cases showed recurrence of pain and abnormal sensitivity "with the same qualitative characteristic as experienced before the operation." Li et al. (2015) [33] studied 10 patients with chronic phantom limb pain after unilateral lower limb amputation and seven other similar amputees with no phantom limb pain. QST showed that the patients in the phantom limb pain group all had lowered pain thresholds in the normal limb, strongly suggesting CS. Vaso et al. (2014) [34] tested the hypothesis that phantom limb pain may be generated in the denervated dorsal root ganglion by injecting local anesthetic into the intervertebral foramen, relieving the phantom limb pain and the nonpainful phantom limb sensation.

These three articles imply sensitization at the dorsal root ganglion level after persistent peripheral nerve injury as a consequence of peripheral sensory nerve transection. However, this situation does not fall within the province of our question, first because the dorsal root ganglion is part of the peripheral nervous system, not the central nervous system; and second because the nerve injury never really heals. There is persistent pain generation in some amputees, insofar as amputation neuroma formation in the peripheral nerve stump is well documented. Even in those patients who do not develop amputation neuromas, the deafferentation of the dorsal root ganglion neurons arguably persists, as even "successful" nerve trunk grafting is highly unlikely to achieve full afferent reconnection. Accordingly, these articles, falling outside the question we were researching, were omitted from all evidence categories.

Evidence Category 2(c): Analysis of Publications Judged to Provide Strong Evidence for the Concept of CS as a PAPG

No publications were judged to fit this definition.

Evidence Categories 2(d) and 2(e): Analysis of Publications Judged to Provide Weak or Strong Evidence Against the Concept of CS as a PAPG (Tables 4 and 5)

We classified 10 publications as providing evidence strongly against CS as a PAPG after injury healing (Table 4) and 61 as providing weak evidence (Table 5). Once again, we encountered the fundamental problem that no publications addressed our question directly. Therefore, we followed the same generous over-inclusive policy we had used in analyzing the "consistent with" publications. These 71 articles are analyzed under the following three headings:

1. Evidence of factors confounding QST, CPM, or CSI measurements
2. Reversibility of QST and CSI measurements with successful surgery or psychological treatments
3. Reversibility of brain changes on fMRI/MRI studies with treatment that relieved symptoms.

1. Evidence of Factors Confounding QST, CPM, or CSI Measurements

Several reviews have cast doubt on the significance of QST, CPM, or CSI test results as indicators of CS, at least in the way that such testing has been conducted to date.

Hubscher et al. (2013) [35] conducted a review of 1,516 studies. They performed a meta-analysis of 145

effect sizes from 40 studies, examining the relationship between pain intensity as measured by QST and self-reported pain or pain-related disability in people with spinal pain. They concluded, "Our study indicates either that pain threshold is a poor marker of central sensitization or that sensitization does not play a major role in patients' reporting of pain and disability."

Backonja et al. (2013) [36] presented the deliberations of the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (NeuPSIG), concluding, "QST is not recommended as a stand-alone test for the diagnosis of neuropathic pain," and further that, "Interpretation of results should always take into account the clinical context, and patients with language and cognitive difficulties, anxiety, or litigation should not be considered eligible for QST."

O'Leary et al. (2017) [37] conducted a systematic review of 13 studies investigating whether nervous system sensitization in peripheral musculoskeletal conditions (as measured by QST) predicts poorer clinical outcomes in response to surgical or conservative interventions. The authors concluded, "This systematic review found insufficient evidence to support an independent predictive relationship between QST measures of nervous system sensitization and treatment outcome. Self-report measures demonstrated better predictive ability."

Longitudinal studies of patients with chronic low back or neck pain [38], acute low back pain [39], and knee pain before and after operation [40] found no/weak predictive association between QST/CSI and the subsequent development of chronic pain. Similarly, Marcuzzi et al. (2016) [41] reviewed 6,408 references, investigating for any link between QST and the development of chronic low back pain, concluding, "it remains unknown whether QST measures are predictive of outcome in LBP [low back pain]."

Several specific factors have been found to confound the responses of human subjects undergoing testing by QST, CPM, or CSI:

- Anxiety and depression
- History of trauma
  - History of abuse
  - Post-traumatic stress disorder
- Pre-morbid personality traits
  - Catastrophization
  - Somatization
  - Other Pre-Morbid Personality Traits
- Fear of pain and low expectations of recovery
- Sleep disorder
- Personal injury claim/compensation
- Genetic/familial transmission of CS predisposition
- Behavioral change in response to reactions of others, particularly spouse.

Anxiety and Depression. There are now many studies demonstrating a strong association of anxiety or depression, particularly pre-morbid depression, with QST, CPM, or CSI testing results [12, 40–49]. However, which is cause and which effect remains an unanswered question from these particular studies and reviews.

Longitudinal studies, however, have attempted to address this question. Schieir et al. (2009) [50] reported that depression in patients with early-stage arthritis "predicted the trajectory of pain." Chaichana et al. (2011) [51] reported that preoperative depression predicted decreased likelihood of a satisfactory outcome after lumbar discectomy. Kroenke et al. (2011) [52], in a longitudinal study of 500 patients with back, hip, or knee pain, showed that an increase in depression was followed by an increase in pain and vice versa. Sinikallio et al. (2011) [53], in a longitudinal study of 96 patients undergoing lumbar spinal surgery, concluded, "Depressive symptoms interfere strongly with the ability of patients to obtain an optimal surgery outcome." Moss-Morris et al. (2011) [54] showed in a cohort of 246 patients with glandular fever that the transition to new chronic fatigue syndrome was significantly more frequent in patients with anxiety, depression, somatization, perfectionism, or negative illness beliefs. Knaster et al. (2012) [55] showed in a longitudinal study of 100 pain clinic patients that 77% of anxiety disorders had been present before pain onset, whereas 63% of the depressive disorders appeared after the onset of pain. Klyne et al. (2019) [56] conducted a 6-month study of patients presenting with acute low back pain and reported that abnormal QST and CPM test results diagnosing CS did not reliably predict the progression to chronic pain.

History of Trauma. History of Abuse. In studies of subjects with nonspecific chronic low back pain [8, 57, 58], healthy children [15], and healthy women reporting varying levels of stressful life events [59], subjects with a history of psychological trauma showed lower pain thresholds, increased hyperalgesia over wider areas, and reduced pain pressure thresholds, irrespective of the type of childhood maltreatment. Even high levels of adversity in childhood result in greater temporal summation in QST [15, 60].

In patients with chronic pain, CSI scores are strongly correlated with major depressive disorder and abuse history [12, 45].

Several studies not using QST or CSI have found strong relationships among chronic widespread pain, CS syndromes (such as fibromyalgia, chronic fatigue syndrome, chronic pelvic pain, and functional gastrointestinal disorders), and childhood adversity and/or abuse [60–63], particularly sexual abuse [62]. Childhood trauma has also been shown to predispose to the development of chronic pain and postsurgical pain [44, 60–63].

In another line of evidence, Dannlowski et al. (2012) [64] studied 148 healthy subjects, screening for psychiatric disorders and measuring amygdala responsiveness by fMRI during challenge with "an emotional face-matching paradigm." They found a strong association

between childhood psychological trauma and amygdala responsiveness to threat-related facial expressions, as well as reduced gray matter volumes. Neither association was influenced by trait anxiety, depression level, age, intelligence, education, or more recent stressful events.

Post-Traumatic Stress Disorder. Several studies have found that post-traumatic stress disorder, especially in individuals who have given military service, strongly influences QST, CPM, and CSI test results [12, 65–67].

In particular, the studies of Moeller-Bertram et al. (2014) [65], Pedler et al. (2016) [66], and McKernan et al. (2019) [67] present evidence linking post-traumatic stress with test results from QST, CPM, or CSI.

Several reviews and studies not using QST or CSI have evidenced the effects of past trauma, including post-traumatic stress disorder, on levels of pain and disability or the development of CS syndromes [11, 44, 64, 68, 69].

Pre-Morbid Personality Traits. Catastrophization. Pain catastrophizing has been strongly linked to pain intensity/hypersensitivity as assessed by QST, CPM, or CSI [47, 70–74]. Other studies not using QST, CPM, or CSI have found catastrophizing to be correlated with pain intensity [42, 44, 75–78] and the development of chronic pain [42, 78]. In a related study, Geva et al. (2014) [79] induced acute psychosocial stress in healthy men and reported that although pain threshold and pain intolerance were unaffected, an increase in temporal summation of pain and a decrease in CPM were observed under stress.

Somatization. Somatization, defined as the expression of psychological stresses through physical symptoms, has been included in the data sets in several studies. It has been reported to be strongly associated with the results of QST, CPM, or CSI testing in survivors of motor vehicle accidents [80], patients with knee osteoarthritis [47], and patients with chronic spinal pain [45]. Somatization has also been found to be a predictive factor for altered CPM performance in patients with chronic musculoskeletal pain [16] and for the development of new chronic fatigue in patients with glandular fever [54].

Other Pre-Morbid Personality Traits. Wynne-Jones et al. (2006) [80] conducted a prospective study of 957 survivors of motor vehicle accidents with a questionnaire assessing pre-collision health, collision-specific factors, post-collision health, and chronic widespread pain. Twelve-month follow-up showed that widespread pain had developed in 7.8% and was strongly associated with post-collision physical symptoms, pre-collision health-seeking behavior, pre-collision somatization, perceived initial injury severity, and older age.

Moss-Morris et al. (2011) [54] studied 246 patients with glandular fever and found that factors that predisposed these patients to develop chronic fatigue syndrome included anxiety, depression, somatization, and perfectionism.

Clark et al. (2019) [81–83] studied 165 patients with nonspecific chronic low back pain using CSI, the Adolescent/Adult Sensory Profile, the State/Trait Anxiety Inventory, and the Marlowe Crowne Social Desirability Scale. In the high-score CSI group, there was a high prevalence of extreme trait sensory hyper- and hyposensitivity profile scores and defensive high-anxious personality type. CSI score increases could be predicted by sensory-sensitive low-registration profiles, trait anxiety scores, and extreme defensive high-anxious personality type.

Fear of Pain and Low Expectations of Recovery. Several studies have shown that QST/CPM test results are correlated with or influenced by fear of pain, pain expectation, or low expectation of recovery. This has been demonstrated in postoperative pain [70, 78], chronic low back pain [84], and chronic musculoskeletal pain [16].

Ferrari (2010) [85] studied 91 whiplash patients within 1 week of their collisions in order to ascertain their expectations of recovery. Patients who expected "never to get better" or who said "don't know" when asked whether they would get better had a much higher likelihood of developing at least one sign of CS 3 months after the collision.

Nir et al. (2012) [86] demonstrated that cognitive manipulation of test subjects' pain expectations with regard to the conditioning painful stimulus changed the magnitude of measured CPM.

In a subsequent study, Nahman-Averbuch et al. (2016) [87] found that reduced efficiency in CPM was associated with higher levels of the harm avoidance trait but not with novelty seeking, reward dependence, state anxiety, or pain catastrophizing.

Studies that did not use QST, CPM, or CSI have reported that low recovery expectations [76, 88, 89], pain catastrophizing and fear of pain [76, 88, 89], and poor self-appraised problem-solving ability [90] were all predictors of chronic pain and disability.

Sleep Disorder. Rabey et al. (2015) [43] studied 294 patients with chronic low back pain and found that QST and CPM results were correlated with female gender, depression, and sleep disturbance.

Koffel et al. (2016) [91], in a study of 250 veterans, found that changes in sleep complaints at 3 months significantly predicted chronic pain at 12 months.

Neblett et al. (2017) [45] studied 763 patients with chronic spinal pain disorder and found that CSI severity groups were significantly related to pain intensity, pain-related anxiety, depressive symptoms, somatization symptoms, perceived disability, and sleep disturbance ($P < 0.001$).

Smith et al. (2019) [92] studied 79 healthy adults with QST after 2 nights of random forced awakenings compared with after 2 nights of uninterrupted sleep. Sleep

disruption increased secondary hyperalgesia in normal males and temporal summation in normal females.

Personal Injury Claim/Compensation. Voorhies et al. (2007) [93] studied 110 adult patients before and after lumbar surgery for identified pain generators and used the Beck Depression Inventory to assess depression. In regression analyses, an independent association was detected between high preoperative depression scores and 2-year disability and symptom severity. Furthermore, the authors observed, "There was no probability of a good or excellent outcome in the presence of either psychiatric factor or personal injury claim, and only a 23% chance with a compensation case."

Other studies have linked poor outcome with injury compensation status [94] and perceived injustice [95–98].

Genetic/Familial Transmission of Predisposition to CS Syndromes. Genetic. Several studies have pointed to the importance of familial transmission of trait hyperalgesia [100]; predisposition to the development of chronic widespread pain [8]; and predisposition to several CS syndromes, including chronic fatigue and fibromyalgia [100–104].

Particularly notable are the large surveys by Kato et al [103, 104] concluding that predisposition to chronic widespread pain and several CS syndromes is "mediated by unmeasured genetic and family environmental factors in the general population. The extent of mediation via familial factors is likely to be disorder specific."

Gender. Female gender has been linked to increased sensitivity in QST/CPM testing [105–107], as well as to predisposition to the development of chronic pain in orofacial pain [108], dental allodynia [109], epicondylalgia [6], shoulder pain [70], chronic widespread pain [8], heel pain [19], chronic low back pain [43], whiplash injury [71], and after sleep deprivation [92].

Behavioral Change in Response to Reactions of Others, Particularly Spouse. There is an extensive body of literature on so-called operant conditioning, dating as far back as 1984 [110], presenting evidence for change in behavior, including pain behavior, in response to the reactions of spouses. The review of Adamczyk et al. (2019) [111] is particularly notable, with other source publications [110, 112–129].

The reason we have catalogued these manifold factors that have been shown to confound human subjects' responses to QST, CPM, and CSI is that almost all human laboratory work on CS has been done with these measurement tools, usually without recognition of the confounding factors, much less controlling for them. Of the 384 human experimental reports that we selected in our 751 publications for intensive study, 186/384 evidenced no consideration of the possibility of extant peripheral nociceptive pain generators, 199/384 evidenced no consideration of secondary gain in the patients studied when it could have been relevant, and 60/141 did not make any attempt to diagnose CS formally in their subjects by QST, CPM, CSI, or the diagnostic algorithm of Nijs et al. (2014) [14]. (In the lattermost category, however, only 60/141 articles were published after 2014.)

2. Reversibility of QST and CSI Measurements with Successful Surgery or Psychological Treatments

The evidence for reversibility of CS presented in these publications was held not to disprove the possibility that CS could persist as a PAPG, but rather to demonstrate clear evidence of reversibility if peripheral pain generation were diminished.

Improvement in the results of nociceptive reflex and other QST or CPM testing has been shown in patients with fibromyalgia randomized to six weekly sessions of telephone-delivered cognitive behavioral training [130], in patients with past trauma history given disclosure therapy [131], and in normal subjects and patients with chronic low back pain given pain-focused cognitive training [17, 132, 133].

De Oliveira et al. (2019) [134] reviewed 52 studies related to pain sensitization and painful knee disorders, with meta-analysis demonstrating that several therapeutic inventions reduced measures of pain sensitization, suggesting reversibility of CS.

3. Reversibility of Brain Changes on fMRI/MRI Studies with Treatment that Relieved Symptoms

Similar to the reversibility of QST and CSI measurements with successful surgery or psychological treatments as described in the previous section, the evidence for reversibility of CS-associated brain structural changes presented in the publications described in this section was held not to disprove the possibility that CS could persist as a PAPG, but rather to demonstrate clear evidence of reversibility.

Several magnetic resonance studies in patients with chronic pain documented reduced gray matter volumes in the anterior cingulate and dorsolateral prefrontal cortex [135–138], as well as the right insular cortex and operculum, amygdala and brain stem [139], and thalamus contralateral to chronic hip pain [140]. Several studies have shown reversal of the gray matter volume reductions after hip surgery [139, 140], surgery for nonspecific chronic low back pain [136], resolution of post-whiplash headache [135], and successful reduction in chronic pain with cognitive behavioral therapy [137, 141].

The evidence in CS syndromes is less consistent, with De Lange et al. (2008) [142] reporting a study of patients with chronic fatigue syndrome in whom significant improvement in lateral prefrontal cortical gray matter volumes occurred in tandem with improvement in cognitive speed after cognitive behavioral therapy.

Reviews of MRI findings in CS syndromes differ in their conclusions. Cagnie et al. (2014) [27] reviewed MRI changes in fibromyalgia, concluding that there was "moderate evidence that central sensitization is correlated with gray matter volume decrease in specific brain regions, mainly anterior cingulate cortex and prefrontal cortex." However, Walitt et al. (2016) [143], after a review on the neuroimaging of five CS syndromes (fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, temporomandibular joint disorder, and vulvodynia syndrome), concluded that "a defining neuroimaging 'signature' cannot be discerned for any of the particular syndromes or for an over-arching central sensitization mechanism common to all of the syndromes."

Discussion

Widely Accepted Manifestations of CS

In the current state of the literature there are three widely accepted manifestations of CS, each generally held to be supported by evidence presented in many peer-reviewed publications.

1. CS in Acute Pain Due to Injury or Disease

We believe this phenomenon has been proven to occur in humans in a proportion of acute pain situations.

2. CS in Some Chronic Pain States in the Presence of Persisting Injury or Disease

Meacham et al. (2017) [144] carried out the only review that approached the question we addressed in our investigation. They reviewed evidence on peripheral and central mechanisms for neuropathic pain and concluded, "While new preclinical evidence supports and expands upon the key role of central mechanisms in neuropathic pain, clinical evidence for an autonomous central mechanism remains relatively limited. Recent findings from both preclinical and clinical studies recapitulate the critical contribution of peripheral input to maintenance of neuropathic pain."

This conclusion mirrors our own—namely, that we have been unable to discover any evidence or combination of different lines of evidence that in our estimation proves that CS after injury can persist in humans as a PAPG after the painful injury has healed.

3. CS as a Possible Constitutional Condition or Predisposition, Leading to Various Complaints of Pain and Other Disabling Symptoms Throughout Life (CS Syndromes), with Insufficient Pain-Producing Pathology Found to Explain the Severity or Widespread Nature of the Pain

This an immense and complex topic and beyond the scope of the present study. Many authors maintain, on the basis of the hypothesis that CS is the underlying pain generator in numerous CS syndromes, that this validates the assumption that CS initiated by a painful injury can persist as an autonomous pain generator even after the injury has healed [5, 10, 11, 16]. This tenuous extrapolation appears unsupported by evidence and may be incorrect even if the primary hypothesis that CS is the underlying cause of fibromyalgia is ultimately proven.

Factors That Subvert Proof of the Hypothesis

We identified four factors in the articles we reviewed that act, individually and together, to subvert proof of the hypothesis which we have tested.

1. The Extrapolation in Many Publications of Laboratory Animal Data to Humans

We analyzed 74 animal study publications, ranging from reports of laboratory studies of single neurophysiological, neuroanatomic, or neurochemical phenomena, to the authoritative reviews of Woolf [5], Latremoliere [7], and others.

Although we appreciate the evidence and discussion of multiple neurophysiological mechanisms by which CS could persist as a PAPG, and we accept that at least some of them could well be operative in the human in pain, we were unable to find a single study that provided proof of the affirmative answer to our question.

2. A Pervasive Fault of Failing to Demonstrate (or, in Many Publications, Even Investigate for) the Absence of Peripheral Pain Generators in Humans

Proving the absence of peripheral pain generators is the most difficult exercise in CS research, and nowhere is this more apparent than in the multitude of studies of CS in subjects with chronic low back pain (74 studies in our final cohort of 751 articles).

Many or most of these studies used QST, including pressure pain thresholds, temporal summation and windup, CPM, and CSI, and reported a significant proportion of subjects to show evidence of CS. We studied these publications in an attempt to discern how these patients were diagnosed as having "nonspecific" chronic low back pain, with the implication of no discoverable peripheral pain generators, but this information is almost never provided. This, to us, raises the fundamental question of whether there may be, in some or all of these subjects, one or more spinal pain generators that might have been diagnosed by a spinal specialist armed with state-of-the-art radiological and electrophysiological investigations. In our view, therefore, it is quite possible that these studies have merely demonstrated CS as a normal phenomenon in a proportion of patients, many or most of whom could have had peripheral nociceptive or neuropathic pain generators driving CS.

Our reflections on this group of much-studied patients apply to a significant proportion of the published literature on CS. The difficulty resides in the question of whether or not

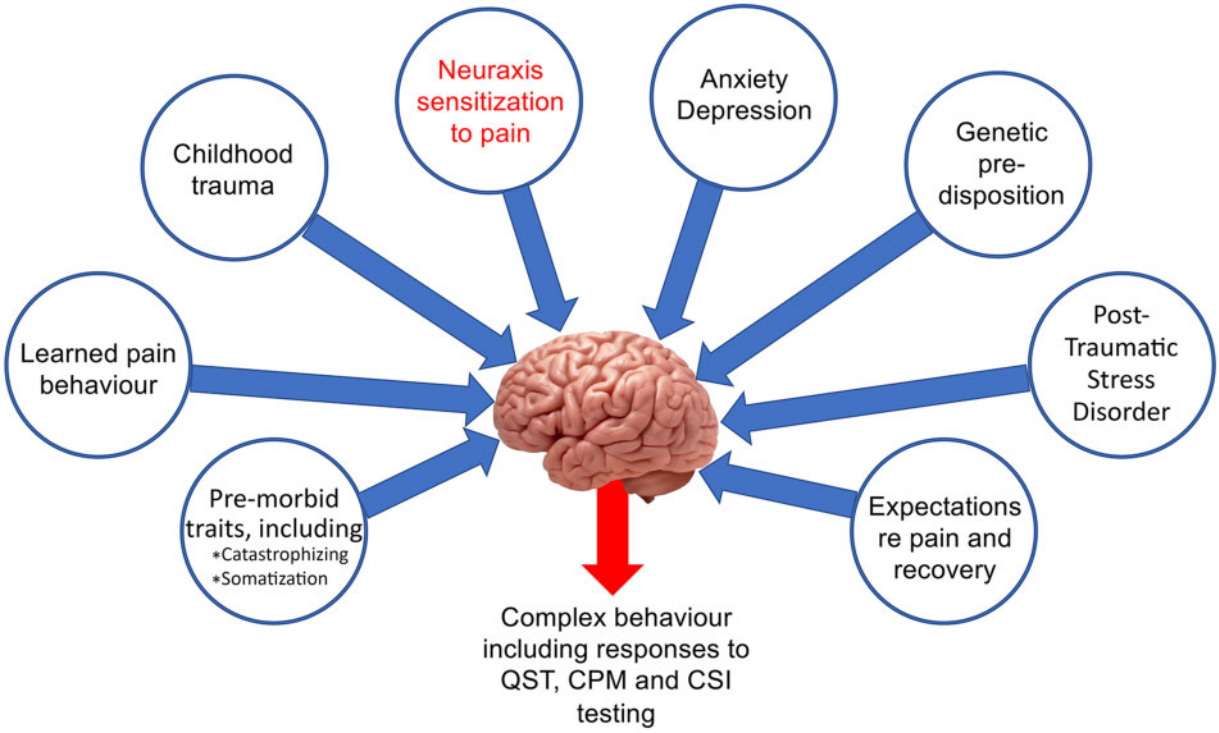

Figure 1. Factors shown to influence responses to QST, CPM, and CSI test results.

occult peripheral nociceptors are perpetuating the CS process, and in this vein, the debate about peripheral pain generators in CS syndromes continues [145–148]. For example, Freeman et al. (2009) [145] and Nystrom et al. (2018) [149] found an immediate rise in pressure-pain thresholds after injection of trigger points with local anesthetic in post-whiplash patients, strongly implying peripheral nociceptors. Haroutounian et al. (2014) [146] demonstrated simultaneous relief of neuropathic pain and reduction of QST/CPM abnormality by peripheral nerve blockade. Argoff et al. (2018) [148] presented an excellent review of this topic, as did Raja et al. (2020) [150], who submitted several lines of clinical and preclinical evidence to support the postulate that chronic neuropathic pain reflects spontaneous and ectopic activity in primary afferent neurons in peripheral nerves and dorsal root ganglia.

3. Recognition of the Factors Confounding Subject Performance in QST, CPM, and CSI

In view of the extensive evidence of psychological and physiological factors confounding assessment by QST, CPM, and CSI, and that the vast majority of the studies that we have reviewed have failed to recognize or control for these factors, we are forced to opine that there is good reason to doubt many of the conclusions. Hansson (2014) [151] presented an authoritative discussion of this matter.

With regard to the diagnosis of CS in an individual patient, the publications of Nijs and co-workers have advocated a diagnostic algorithm for CS [15], as well as use of the CSI [12, 13, 152–157]. From our review of these and other publications, we find that the diagnosis of CS in an individual patient rests solely on only two elements: widespread pain (which may include multiple tender pressure points and allodynia) and a CSI score >40. We believe this now to be arguably tenuous.

4. The Gradual Change in Our Understanding of What is Being Measured by QST, CPM, and CSI

The publications analyzed above collectively constitute a transforming body of evidence that has greatly expanded the concept of CS from a purely neurophysiological phenomenon, as demonstrated in animal research, to one admitting the overarching influence of the "head ganglion" or cerebrum in humans.

After our comprehensive review of relevant literature, we conclude that the concept of what is being measured by QST, CPM, and CSI is best regarded as in Figure 1.

Devor (2001) [158], in his obituary of Patrick Wall, quotes Wall as saying of pain in humans, "Pain is an unpleasant sensory and emotional experience …, with the stress on experience. It is a thing that can exist only in a conscious brain. Pain, per se, does not exist at the level of the molecule. The study of pain must not lose sight of mind." We have found from our extensive review that there is now overwhelming evidence to support Wall's statement.

Conclusions

We have been unable to discover any evidence, or combination of different lines of evidence, that in our

estimation proves that CS after injury can persist in humans as an autonomous pain generator after the painful injury has healed. Our review has also shown that the evidential basis for the diagnosis of CS is seriously in question.

Limitations

Lack of proof of the hypothesis we tested does not constitute proof of its falsity. However, if CS is to be proved to be capable of acting as a PAPG, advocates will have to contend with the multitude of factors now shown to influence subjects' performances in QST, CPM, and CSI, as discussed in the foregoing, and will have to address the most difficult of questions—that of whether the demonstrated CS continues to be driven by occult peripheral pain generators.

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