Cognitive Impairment in Patients with Chronic Pain: The Significance of Stress

Robert P. Hart, PhD, James B. Wade, PhD, and Michael F. Martelli, PhD

Address
Department of Psychiatry, VCU Health System, P.O. Box 980268, Richmond, VA 23298-0268, USA.

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This review article examines the role of emotional distress and other aspects of suffering in the cognitive impairment that often is apparent in patients with chronic pain. Research suggests that pain-related negative emotions and stress potentially impact cognitive functioning independent of the effects of pain intensity. The anterior cingulate cortex is likely an integral component of the neural system that mediates the impact of pain-related distress on cognitive functions, such as the allocation of attentional resources. A maladaptive physiologic stress response is another plausible cause of cognitive impairment in patients with chronic pain, but a direct role for dysregulation of the hypothalamic-pituitary-adrenocortical axis has not been systematically investigated.

Introduction

This article discusses studies that examine cognitive functioning in patients with chronic pain with an emphasis on the role of emotional distress and the mechanisms of stress-related effects. The prevalence of chronic pain (*ie,* persisting for at least 6 months) in the general US population has been estimated to be in the range of 35 to 75 million [1]. Cognitive dysfunction is one component of the behavioral change that can occur in this common clinical condition. Chronic pain and associated symptoms complicate the presentation of other patients, including those with documented or presumptive brain injury. Although clarifying the impact of momentary pain is important, the concomitants of chronic pain, such as mood change, sleep disturbance, fatigue, and other aspects of suffering (*eg,* lifestyle interference secondary to disability), seem to be more closely related to cognitive impairment.

Sensory-discriminative and affective-motivational components of pain appear to be processed in parallel by different parts of the nociceptive system [2•,3,4]. Medial thalamic nuclei, the anterior and mid-cingulate, and related structures appear to mediate the affective-motivational component of pain. Some of the brain structures involved in processing affective-motivational dimensions of pain presumably are components of the neural system mediating the impact of pain-related stress on cognitive functioning.

Previous reviews have concluded that chronic pain is commonly associated with neuropsychologic impairment [5•,6]. Impairments are most evident on tests assessing attentional capacity, processing/psychomotor speed, and memory. Although many of the previously reviewed studies assessed emotional status or used symptom inventories that included items pertaining to characteristics such as fatigue, mood state, and distress, few studies have systematically explored the relationship between these variables and neuropsychologic test performance. The next section summarizes studies that have not been previously reviewed by Hart *et al.* [5•]. A later section focuses on previously reviewed and more recent studies that specifically address the role of psychologic distress and mood disturbance on cognition in patients with chronic pain.

Recent Neuropsychologic Findings in Chronic Pain Populations

A study of more than 100 patients with head, neck, or back pain who experienced decreased mental and physical functioning [7] underscores the importance of clarifying whether a patient with chronic pain is seeking financial compensation. Twenty-nine percent of those seeking financial compensation, but none of those not seeking compensation, failed two or more of the six neuropsychologic tests used to detect malingering. Heyer *et al.* [8] observed patients before and after they underwent lumbar spine surgery; 12.5% had suffered a previous stroke or transient ischemic attack, 8.3% had undergone carotid endarterectomy, and 42% were administered analgesic medications after surgery. Rated pain intensity correlated with performance on Trail-Making Part A and the Rey Complex Figure Test (RCFT) after the surgery, but not before; however, the relationship between pain intensity and RCFT performance was potentially confounded by medication use. Two other test measures did not correlate with rated pain intensity (Controlled Oral Word Association, Trail-Making Part B). Park *et al.* [9] compared patients with fibromyalgia recruited from a university-based clinic with healthy control subjects. Patients with other significant health conditions or major psychiatric disorders,

including depression, were excluded. The patients were impaired on measures of working memory capacity (reading span and computation span), free recall of a 16-item word list, and yes-no recognition memory of a word list and vocabulary, and performed marginally worse on a measure of verbal fluency. Measures of pain symptomatology, but not of mood or fatigue, correlated with performance on the working memory capacity and verbal memory tests. The patients were not impaired on measures of information processing speed (number, pattern, and letter comparison); however, these tests were simple and brief (*eg,* stimulus strings of three to nine segments and 30-second trials) compared with other tests of information processing speed that have been used to assess patients with chronic pain (*eg,* Paced Auditory Serial Addition Test [PASAT]). Furthermore, a measure of pain-related daily dysfunction correlated with the patient's performance on these measures of information processing speed and with performance on the tests of working memory capacity and verbal memory. Some of these investigators [10•] subsequently reported deficits in patients with rheumatoid arthritis on similar letter and pattern comparison tests of information processing speed in association with higher levels of pain and depression.

A negative finding in a small sample of 10 control subjects [11] is consistent with the type of clinical features identified in an earlier review [5•] that are most likely to be associated with pain-relative cognitive impairment. All 10 subjects were engaged in their normal work activities and had pain symptoms that were localized to one shoulder; the pain did not involve multiple sites or the head, neck, or back region. Pain was of low intensity (median visual analog scale [VAS], 9%) and as short as a 3-month duration. The Hopkins Symptom Checklist (SCL) did not indicate any mood changes or tendencies toward somatization. The three cognitive tests that were administered were brief (5 minutes). The pain group reported a higher level of perceived stress during the tests than the control subjects did, raising the possibility that deficits might have occurred if the tests were more cognitively demanding.

The Role of Emotional Factors and Chronic Stress

The effects of pain on cognitive functioning are not related in a simple fashion to its immediate sensory-discriminative features (*ie,* intensity and location) because the concomitants of chronic pain are the more important mediating variables [5•]. Specifically, cognitive impairment in patients with chronic pain has been associated with mood changes and emotional distress and with symptoms and clinical features such as increased somatic preoccupation, sleep disturbance, fatigue, and perceived interference with daily activities that are potential sources of chronic stress. A "cervicoencephalic syndrome," including dizziness, blurred vision, disturbed adaptation to light, and frequent headache, tends to be associated with cognitive impairment, perhaps as a result of chronic stress because even routine activities often require concentrated effort. The trend toward greater impairment for patients with post-traumatic pain (without evidence of brain injury) than for patients with other forms of pain also is suspicious for the influence of chronic stress related to perceived victimization.

Models of pain processing that distinguish the sensory, affective, cognitive-evaluative, and behavioral dimensions facilitate our understanding of the effects of chronic pain on cognitive functioning. The model that has guided our research distinguishes several stages of pain processing [12,13•,14]. The first stage, a sensory dimension, is commonly assessed by ratings of pain intensity. The second stage or immediate affective response commonly is assessed by ratings of pain unpleasantness. The third stage relates to the meaning and implications of pain for the patient and thus to associated emotional suffering, and is commonly assessed by measuring pain-related emotional states (*eg,* depression, anxiety, frustration) and beliefs (*eg,* perceived ability to endure pain). The fourth stage refers to illness behavior that can be assessed through ratings (*eg,* lifestyle interference) or observed by the examiner or collateral sources (*eg,* pain behaviors manifested at home or during clinical interview).

Considerable research, including studies reviewed in this article and previously [5•], has established that emotional distress frequently accompanies chronic pain. Emotional distress is related partly to specific symptoms, such as sleep disturbance, that are common in chronic pain [15]. Perhaps more importantly, mood change and chronic stress are not surprising because of the restrictions in daily activities, disruptions in preferred role functions, losses of sources of satisfaction and reinforcement, and changes in one's sense of identity and self-esteem that can occur because of chronic pain [16]. Avoidant behavior and reduced activity level can perpetuate a cyclic disability-enhancing pattern of further avoidance in activity and associated emotional distress. For example, Chapman and Gavrin [17] emphasize the distinction between pain and suffering. Suffering entails a disparity between what people believe themselves to be and what people are, which often occurs with poorly controlled chronic pain. Associated psychologic stressors may include feeling a loss of control, hopelessness, fear, and other negative beliefs and attributions. The idea that one's pain is uncontrollable is in itself a stressor. In addition to the stressors of pain and associated negative thinking, sustained maladaptive physiologic stress responses may leave a person feeling sick (*ie,* produce or exacerbate fatigue, dysphoria, muscle aches, sleep disturbance, somatic hypervigilance, and mental inefficiency).

Cognitive complaints for patients with chronic pain are more closely related to measures of emotional distress than to sensory-discriminative aspects of pain, and are

associated with motivational changes, such as a reduced desire for activities [18–20]. The following section discusses studies that relate cognitive impairment to emotional distress and later stages of pain processing.

Several studies have shown that psychologic distress and negative emotions are more closely associated with cognitive deficits in patients with chronic pain than is pain severity. Kewman *et al.* [21] found correlations between ratings of pain intensity, psychologic distress (composite measure of depression, anxiety, irritability, and energy level), interference with daily activities, and a composite score from a cognitive screening measure. When the effect of distress was partialed out, pain ratings no longer correlated with test performance. Grace *et al.* [22] found that pain intensity and trait anxiety (but not depression) correlated with measures of memory and processing speed. When the effect of mood was partialed out, pain intensity no longer correlated with test performance; however, after the effect of pain intensity was partialed out, trait anxiety still correlated with the Wechsler Memory Scale (WMS)-Revised Delayed Recall Index. Landro *et al.* [23] reported that only those patients with a history of major depression had memory impairments, and their rated pain intensity did not correlate with their test performance. Radanov *et al.* [24] found that poor performance on a test of processing speed was associated with lower ratings of emotional well-being and higher levels of self-reported nervousness. In a follow-up study [25], those patients who remained symptomatic and evidenced subtle attentional impairments 6 months and 2 years later continued to rate their emotional well-being lower. Because the latter studies did not include ratings of pain intensity, it is unclear to what extent psychologic distress predicted performance decrements independent of pain severity.

Studies that screened patients with chronic pain for psychiatric illnesses or otherwise that had a narrow range of scores on measures of psychologic distress did not find such associations, suggesting that distress or mood disturbance is only one factor that may contribute to cognitive impairment. For example, Eccleston [26,27] did not find an association between measures of distress from the McGill Pain Questionnaire or of mood disturbance (anxiety, depression) and performance on an attention-demanding numerical interference tasks, but his patients with pain had been screened for treatment of depressive symptoms and "severe emotional problems." In fact, his patients and control subjects had a similar frequency of mood disturbance [27]. Taylor *et al.* [28] reported subtle impairments in processing speed and short-term memory in two different groups of patients with chronic pain. Pain intensity and depression levels did not correlate with test performance, but the authors point out that there was a narrow range of scores on both measures.

Other findings suggest that psychologic distress or suffering in the form of increased somatic awareness or preoccupation is associated with cognitive deficits in patients with chronic pain. Eccleston *et al.* [29] found that only those patients reporting high somatic awareness (operationalized as a greater frequency and breadth of diffuse somatic complaints on a questionnaire) and higher pain intensity were impaired on a version of their attention-demanding numerical interference task. These patients also reported higher levels of depression and anxiety; however, the relationship between the level of emotional distress and test performance was not examined. Other studies have found associations between the level of somatic complaints and cognitive performance in patients with chronic pain, although clinical features that may covary with somatic complaints were not explored systematically. Patients whose temporomandibular disorder (TMD) occurred after a cervical whiplash injury (without a loss of consciousness) reported more somatic complaints on a modified SCL-90 and exhibited more impairment on tests of simple and choice reaction time and memory than patients with idiopathic TMD [30]. However, chronic pain related to whiplash injury may be relatively more severe and widespread [30] or associated with additional symptoms, such as dizziness and blurred vision [24]. Even if litigation is not a confounding issue, emotional reactions and negative attributions related to feelings of victimization also may be important factors. Furthermore, the study by Goldberg *et al.* [30] did not explore the relationship between emotional status and cognitive function. Cote and Moldofsky [31] found that the endorsement of somatic items from a depression scale covaried with ratings of pain intensity and fatigue, and with performance on a simulated multitask office procedure. None of these studies explored whether increased somatic awareness or complaints uniquely contributed to cognitive impairment. Nevertheless, these findings suggest that a somatic focus and associated emotional reactions may increase the disruptive influence of pain on cognition by facilitating access of pain into awareness [29].

Recent studies of patients with chronic pain implicate emotional distress and the later stages of pain processing in relation to cognitive impairment. Iezzi *et al.* [32] evaluated patients with chronic pain who were recruited consecutively from a hospital-based pain service. Pain was musculoskeletal in nature (*eg,* fibromyalgia, myofascial, osteoarthritis), and included patients with multiple pain sites and involvement of the neck or head. Approximately 50% of the patients were taking two or more classes of medication, including opioids. Patients with cancer, neuropathic pain, a history of major psychiatric illness or a history of traumatic brain injury (TBI), or other neurologic disorder affecting brain function were excluded. Statistical clustering procedures were used to identify groups reporting high, moderate, and low levels of emotional distress based on their SCL-90-R profiles. Those patients highest in emotional distress exhibited deficits in attention and processing speed (*eg,* Stroop Test, PASAT), memory (WMS-R Logical Memory and Visual Reproduction),

nonverbal intelligence (Wechsler Adult Intelligence Scale-Revised), and executive functions/abstraction (Wisconsin Card Sorting Test, RCFT Copy) compared with those patients lowest in emotional distress. The performance of the moderately distressed group tended to be intermediate to the other two groups. Deficits were not related to pain intensity ratings, disability/legal status, or medications. Wade and Hart [33] reported findings on the Digit Span Test in a large sample of patients with chronic pain (n = 736) consecutively evaluated at a pain management clinic in a medical center. Approximately 50% of the patients suffered from low back pain. The second and third most frequent diagnoses were myofascial dysfunction and complex regional pain syndrome. Most patients reported multiple pain sites. Patients with cancer-related pain or a history of TBI or neurologic disorders affecting cognition were excluded. The multidimensional aspects of pain were evaluated according to the four-stage model of pain processing. Patients completed VASs of pain sensation intensity (stage 1), pain-related unpleasantness (stage 2), and emotional states and negative illness beliefs associated with suffering (stage 3). A structured pain interview was used to assess illness behavior (stage 4). Step-wise multiple regression analyses were completed using measures of each pain stage as predictors and digit span as the criterion. A final regression analysis using only those predictor variables reliably related to attention in the first set of analyses indicated that measures of pain-related depression, perceived lifestyle interference, and the degree of social reinforcement for pain-related behavior were uniquely related to the deficits in attention span. Deficits were not related to pain intensity. Maladaptive beliefs and negative thoughts relating to perceived lifestyle interference contributed to pain-related suffering. Social reinforcement of pain behaviors (*eg,* solicitous responses) may serve to further increase somatic focus or preoccupation and, secondarily, psychologic distress. A subset of these patients (n = 274) also were administered the Verbal Paired Associate Learning subtest of the WMS. Similar analyses revealed that deficits in verbal learning were associated with pain-related anxiety after controlling for pain sensation intensity [34].

Brown *et al.* [10•] evaluated a large community-dwelling sample of patients with rheumatoid arthritis (n = 121). Measures of cognition included two tests of processing speed (timed letter comparison and pattern comparison), an inductive reasoning test that asked patients to determine the rule that made four of five sets of letters alike, two tests of working memory capacity (reading span and computation span), and the free recall of two lists of 25 words. Two scales were administered that assessed pain intensity (*eg,* pain at different times of the day, after physical activity) and some aspects of suffering or later stages of pain processing (how often pain interfered with activities). A composite measure of depression was derived from subscales of different instruments. High levels of pain and depression were associated with poor cognitive performance in all four areas of functioning (information processing speed, working memory capacity, reasoning ability, and verbal memory). Structural equation modeling indicated that depression mediated the relationship between pain and cognitive functioning (*ie,* chronic pain causes depression, which causes impairment in cognitive functioning). The effects of pain on cognition were no longer significant after controlling for depression. A model with "paths" from pain to depression and from depression to cognition, but not from pain to cognition, explained 55% of the variance in general cognition.

Although the study by Park *et al.* [9] did not find significant correlations between measures of depression and anxiety and cognitive performance, their findings are consistent with the role of later stages of pain processing in the cognitive impairment of patients with chronic pain. As the authors point out, their patients with fibromyalgia were screened carefully for depression; the mean symptom scores were below the cutoffs for even mild depression. Cognitive performance across multiple domains correlated with scores on a pain subscale that primarily measured the functional impact of pain; however, they did not correlate with scores on a pain questionnaire that measured pain intensity in a more focused manner [9]. The functional impact of pain is related in large part to its meaning and the implications for the patient (stage 3) and to resultant behavioral changes (stage 4). Pain-related suffering associated with maladaptive beliefs and with ongoing lifestyle disruption may not be reflected fully in a patient's current mood state.

The often observed relationship between measures of psychologic distress or negative emotions and cognitive performance for patients with chronic pain is perhaps not surprising because of the literature relating depression and anxiety to cognitive impairment. For example, two recent meta-analytic review articles indicate global neuropsychologic impairment in patients who are depressed. Veill [35] found effect sizes ranging from a standard deviation of 0.81 to 0.97 for measures of psychomotor speed (*eg,* Digit Symbol), verbal and nonverbal memory, and visuospatial/visuoconstruction. Veill also found an effect size of 2.0 for measures of mental speed and flexibility (*eg,* Trails B, Stroop Test) [35]. Christensen *et al.* [36] found an average effect size of 0.63 of a standard deviation after performing a wide range of neuropsychologic tests. The largest effect sizes by test category included "attention and tracking" (0.98), "memory mixed" (1.01), and vigilance (1.20). Effect sizes of approximately 1.0 or higher were found for such tests as Digit Symbol, Stroop Test, Benton Visual Retention Test, Buschke Selective Reminding Test, Animal Naming, and the Category Test. For patients with mild depression, the average effect size was 0.21. Prevalence rates for depression in clinic-based chronic pain samples range from 30% to 60% [37]. Some of the brain regions involved in processing the affective component of the pain

experience (anterior cingulate cortex [ACC]) also appear to play a role in the cognitive induction of negative affect in depression. The ACC is integrated with the dorsolateral prefrontal cortex, which is implicated in executive dysfunction in depressive illness [38].

Cognitive impairment and especially memory deficits have been found in combat-related and abuse-related posttraumatic stress disorder (PTSD) [39], and in rape survivors with PTSD who were screened for comorbid psychiatric illness, substance abuse [40], and other anxiety disorders, including obsessive-compulsive disorder, panic disorder, and social phobia [41–44]. Although memory deficits were most common, variable impairment was found for other abilities, including divided attention and executive functions. Studies of healthy subjects indicate that anxiety can negatively impact working memory and information processing [45], learning and memory [46,47], abstraction and problem-solving [47,48], and response inhibition [49], suggesting that subclinical levels of anxiety can be sufficient to interfere with functioning. Patients with chronic pain conditions often report anxiety levels that do not fall within the normal range; a significant amount of the variance in reported pain may be explained by anxiety [50–52]. In a recent study [53], patients with high anxiety reported greater affective responses to cold pressor pain and higher levels of sensory pain, suggesting that anxiety may predispose otherwise healthy people to have negative responses to painful events. Ploghaus *et al.* [54] compared activation responses with thermal stimuli using functional magnetic resonance imaging (fMRI) while varying visual signals to moderate anxiety level. One visual signal (low-anxiety condition) was followed consistently by thermal stimulation of moderate intensity. A second visual signal (high-anxiety condition) was followed by the same noxious stimulation on most trials, but occasionally by a much stronger thermal stimulus. The entorhinal cortex of the hippocampal formation (an area important for memory) responded differentially to the same thermal stimuli, depending on whether anxiety was induced; the activation pattern predicted activity in other brain regions associated with affective pain processing (perigenual cingulate) and intensity coding (mid-insula). The entorhinal cortex may be part of the neural network that mediates the impact of pain-related emotional distress on cognitive functions such as memory.

Neuroanatomic Correlates and the Role of Stress Responses

Anterior cingulate cortex

Neuroimaging studies involving patients with clinical pain consistently have shown changes at the ACC, including areas associated with the emotional response to pain [2•,55]. The ACC is an area of the brain involved in the integration of affective-motivational dimensions of experience and various cognitive processes [56,57]. The affective subdivision of the ACC has connections to structures such as the amygdala, anterior insula, and orbitofrontal cortex and has been implicated in the modulation of affective states and emotional responses and in the evaluation of the emotional valence and motivational salience of information. For example, emotional responses (*eg,* fear and pleasure) may follow electrical stimulation in healthy subjects. Cingulectomy and cingulumotomy have been used to treat patients with pathologic aggression, obsessive-compulsive behaviors, and depression. Activation of this region has been associated with emotional processing (*eg,* recognition of affect in facial expressions, responding to emotionally valenced words) and symptom provocation in patients with psychiatric disorders. In contrast, the cognitive subdivision of the ACC has connections to structures such as the lateral prefrontal cortex, parietal cortex, and premotor areas and has been implicated in the executive control of attention, effortful information processing, and response selection, particularly under conditions that involve novelty, divided attention, conflicting information, working memory, or error detection. This area also is implicated in motor intention/control. Fernandez-Duque and Posner [58] emphasize the role of the ACC in "executive attention" that involves task switching, inhibitory control, error detection, processing novel stimuli, executing novel actions, and allocating attentional resources. Not surprisingly, activity is increased at the ACC in anticipation of a cognitively demanding task.

In regards to attentional control and pain processing, the ACC is part of a cortico-thalamo-mesencephalic network mediating selective attention to painful stimuli, but also is involved in attentional shifting [59]. The latter investigators found that painful stimulation during an auditory discrimination task intended to divert attention from pain produced a regional cerebral blood flow (rCBF) increase only in the mid-part of the ACC. The areas of the ACC involved in orienting responses to painful stimuli and those activated in response to increasing pain unpleasantness appear to be adjacent [60].

The integration of emotional and cognitive self-regulation at the ACC appears to include the executive control of attentional resources under conditions producing emotional distress [56,58,61]. For example, the ACC is activated after error detection or negative feedback, and is the likely source of an event-related potential called error-related negativity. This error-related activity partly reflects the level of motivation for error detection (and thus the allocation of attentional resources) and also is correlated with negative affect (and thus the amount of distress associated with making an error). The amount of the stress associated with making an error seems to depend on the personality dimension of "negative emotionality," which corresponds to the construct of trait neuroticism.

As an area of the brain that modulates emotional reactivity and contributes to the executive attentional system, it is not surprising that the ACC plays a role in pain process-

ing and appears to be an integral component of neural systems mediating the impact of pain-related stress on cognitive functioning. Specifically, the ACC may mediate the affective-motivational and cognitive-evaluative components of the pain experience related to suffering and the allocation of attentional resources under conditions of pain-related emotional distress. The activation of the ACC appears to reflect the degree of pain-related distress experienced [62]. The latter investigator had subjects immerse their hand in water under hypnotic suggestions for increased or decreased pain-related unpleasantness. Positron-emission tomography (PET) scans revealed greater activation during the condition of increased unpleasantness compared with the condition of decreased unpleasantness only in the ACC. Patients with chronic pain treated successfully with cingulumotomy may continue to experience painful sensations, but not the associated emotional suffering; anxious patients tend to be more likely to benefit from the surgery [63].

It has been speculated that, because of the extent to which the ACC is involved in pain processing and attentional mechanisms, the competitive demand may interfere with cognitive functioning [34]. Because painful stimulation and related emotional distress are attention-demanding, the reserved capacity of the ACC to allocate attentional resources may be limited. The plausibility that competitive demand on finite attentional resources may be expressed at the ACC is supported by neuroimaging studies. PET scan findings suggest that the interference effects in performing two attention-demanding tasks simultaneously can occur centrally at the ACC or prefrontal regions [64]. The areas of the ACC that are activated by painful stimuli partially overlap those activated during orienting responses and target detection [2•]. Another study found substantial ACC regional activation overlap on PET scans when patients performed a task that required sustained and divided attention during noxious heat stimulation [65].

The meta-analytic study of Bush *et al.* [56] indicates that the cognitive subdivision of the ACC is activated by various attention and cognitive-demanding tasks, and deactivated (*ie,* reduced blood flow or fMRI signal) by tasks that relate to emotional content; the affective subdivision shows the opposite pattern of activation and deactivation. The suppression of the cognitive subdivision during tasks with emotional content (and vice versa) may be a mechanism involving the ACC by which emotional distress disrupts attentional control and cognitive efficiency. In particular, cognitive subdivision activity may be suppressed during pain-related distress or the processing of the affective-evaluative components of the pain experience (*ie,* suffering). Depressive illness, experimentally induced emotional states in healthy subjects, and the anticipation of pain have all been associated with the deactivation of the cognitive subdivision of the ACC [56]. Because of the identified role of the cognitive subdivision of the ACC, effortful information processing likely is to be disrupted with pain-related distress, whether by mechanisms related to competitive demand on finite attentional resources or reciprocal suppression. These information processing demands include those related to the proposed role of the ACC in responding to pain (*eg,* selecting and organizing motor responses and mediating the learning associated with prediction and avoidance of noxious stimuli) [57]. In addition to its role in information processing, there is some evidence that the ACC contributes to a memory system [66,67]. Memory processes may be potentially disrupted with pain-related distress by the same mechanisms of competitive demand, interference, or reciprocal suppression at the ACC.

Stress-mediated mechanisms

The effects of chronic stress on cognition and the mechanisms by which stress results in changes in brain structure and function have important implications for cognitive functioning in patients with chronic pain. Manifestations of chronic stress, including excessive sympathetic nervous system activity, neuroendocrine response, and possibly immune system activity, may be part of a maladaptive response in patients with chronic pain [17]. Dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis has been associated with mood disorders and PTSD, presumably reflecting the effects of chronic stress or maladaptive stress responses for patients with these disorders. Furthermore, patients with mood disorders and PTSD have reductions in brain volume, particularly in the region of the hippocampus [39,68,69]. For patients with a history of recurrent major depression, hippocampal volume showed an inverse correlation with the total days the patients were depressed [69]. The idea that chronic stress may produce reductions in brain volume is supported by recent findings in healthy control subjects [70]. Trait neuroticism, which reflects the general tendency to experience negative emotions or "stress reactivity" (as characterized by these investigators), showed a negative association with the ratio of the brain to the remainder of intracranial volume. Specifically, the tendency to experience anxiety and negative emotions (*eg,* shame or embarrassment) in social situations was related to reductions in brain volume. The authors note that trait neuroticism has been associated with hypercortisolemia and with an increased future incidence of affective and anxiety disorders. It has been reported that 20% of patients with chronic pain from a multidisciplinary pain program met predefined criteria for one of four McGill-Melzack Pain Index pain subgroup classifications ("emotionally overwhelmed") and had elevated scores on the same measure of trait neuroticism [71].

A considerable amount of evidence exists that implicates chronobiologic dysregulation of the HPA axis in patients with chronic pain. Elevated cortisol levels and reduced melatonin concentrations in patients with cluster and migraine headaches [72,73] have been interpreted as a disorder of hypothalamic circadian function [74]. In a

study of patients with TMD pain, Korszum *et al.* [75] found markedly increased daytime cortisol levels and a 1-hour phase delay in the timing of maximum cortisol levels relative to control subjects. Findings in patients with fibromyalgia include normal to increased plasma adenal glucocorticoid secretion in the morning and evening, but low 24-hour urine-free cortisol levels and an exaggerated pituitary response to challenge testing [76]. Extended studies at 10-minute intervals over a 24-hour period found significant differences in the pattern of circadian secretion of adrenocorticotropic hormone and cortisol, with a general hypoactivation. Crofford [77] has reviewed evidence of HPA axis involvement in acute and chronic pain, including the fibromyalgia spectrum of somatic pain and rheumatic diseases. Ehlert *et al.* [78•] noted that, in contrast to HPA axis hyperactivity in depression, the findings for PTSD, chronic fatigue, and stress-related bodily disorders, such as idiopathic pain syndromes, frequently suggest diminished HPA activity. Thus, findings of HPA dysregulation in chronic pain include hyperactivity and hypoactivity. This is consistent with a chronobiologic disturbance characterized by aberrant HPA activity and cortisol levels that are variably higher and lower in patients with chronic pain than in control subjects over the course of a day, and complex interactions with other neuroendocrine functions, especially those relating to melatonin, serotonin, and endogenous opioids [79].

Additional evidence of dysregulation of the HPA axis in pain syndromes comes from studies examining treatment effects for acute and chronic pain. Specifically, pain relief is associated with reduced cortisol levels and HPA activity. For example, local anesthesia can reduce immunologic and hormonal responses (*ie,* increases in plasma epinephrine and serum cortisol) to acute painful stimulation [80], and septal stimulation-inducing analgesia can produce a decrease in plasma cortisol and in gastric ulceration [81]. Preoperative acupuncture can reduce postoperative pain and nausea and plasma cortisol and sympathoadrenal system activity in patients who have undergone surgery [82]. Sugano and Nomura [83] found that water exercise and stretching programs produced lower salivary cortisol, subjective pain, and anxiety scores in patients with chronic low back pain. Bellometti and Galzigna [84] found that a combination of mud pack and antidepressant treatment positively rebalanced the stress response system, reduced pain symptoms, and improved the quality of life in patients with fibromyalgia. Pizzoferrato *et al.* [85] found that a single thermal mud treatment significantly decreased plasma cortisol and pain complaints for patients with osteoarthritis. Microcurrent cranial and body area stimulation studies have shown elevated plasma serotonin, β-endorphin, γ-aminobutyric acid, and dehydroepiandrosterone, along with diminished levels of cortisol and tryptophan and concomitant improvements in symptoms of pain, insomnia, and depression [86].

The hypothesis that maladaptive stress responses may be a cause of cognitive impairment in patients with chronic pain is plausible because of the evidence for a link between stress-related dysregulation of the HPA axis and neuronal plasticity. McEwen [87] reviewed animal and human research that supports a link between stress and neuronal plasticity at the hippocampus. Repeated stress suppresses neurogenesis of dendate gyrus neurons and produces atrophy of dendrites in the CA3 region. Dendritic atrophy appears to be the result of excitatory amino acid (glutamate) release during repeated stress, which is facilitated by circulating adrenal steroids. Chronic adrenal steroid (*eg,* glucocorticoid) exposure increases *N*-methyl-D-aspartate (NMDA) receptor binding. Serotonin released in response to stress also may facilitate excitatory amino acid activity at the NMDA receptor. Glutamate is a key neurotransmitter that mediates central nervous system hypersensitivity, including sensitization associated with chronic pain [88–90]. Glutamate increases intracellular levels of calcium ions (Ca^{2+}), which has been linked to excitotoxic effects. Sheline *et al.* [69] suggest that, in addition to glucocorticoid-induced neurotoxicity, other potential mechanisms include corticotrophin-releasing factor neurotoxicity and the loss of neuroprotective brain-derived neurotrophic factor.

Traumatic stress and elevated adrenal steroids are associated with signs of atrophy in the human brain [87], but reductions in brain volume in psychiatric disorders such as PTSD and recurrent major depression suggest that the human hippocampus is particularly sensitive. Prolonged glucocorticoid exposure reduces hippocampal cell number [91]. Chronically elevated levels of glucocorticoids in healthy elderly subjects may be associated with hippocampal atrophy [92]. The hippocampus is a primary target for adrenal steroids. Increased glutamate production and release in response to HPA activation has been implicated in reduced hippocampal volume in patients suffering from anxiety and depressive disorders [93,94]. A metabotropic glutamate receptor antagonist (2-methyl-6-phenylethynyl-pyridine) has been shown to possess antidepressant and anxiolytic properties [95]. In patients who are depressed, volume loss in the hippocampus correlates with volume loss in the core nuclei of the amygdala where glutamatergic pyramidal cells predominate [69]. The latter author suggests that over-excitation in one structure can produce damage in the other through reciprocal connections between the hippocampus and amygdala.

Animal models of stress-induced atrophy suggest that periodic HPA axis activity is sufficient to cause damage [87]. McEwen [87] postulates that repeated HPA and associated autonomic and neurochemical reactivity to experiences in the course of PTSD and recurrent depressive illness may underlie progressive neuronal structural changes and eventually cell loss. This same explanation would seem consistent with evidence of reduced brain volume in patients high in trait neuroticism who tend to

experience more life events as stressful and are more susceptible to psychologic distress.

Regional brain volume loss hypothesized to be a consequence of repeated stress and elevated cortisol levels have been associated with cognitive impairment in human subjects. For example, Bremner [39] reported that deficits in memory correlated with decreases in hippocampal volume in one of their PTSD patient samples; Sheline *et al.* [69] found impaired verbal memory and smaller hippocampal volumes in patients with a history of recurrent major depression who were in remission. Administration of the endogenous glucocorticoid cortisol can impair memory function in healthy subjects [96,97]. Newcomer *et al.* [97] did not find effects for tests of sustained or selective attention, but Kirschbaum *et al.* [96] found effects for tests that required spatial thinking and memory (judgements about spatial location after mental rotation or reversal of direction). Memory deficits occur in association with stress-induced (*eg,* public speaking, mental arithmetic) cortisol elevations in healthy subjects [96,98]. Lupien *et al.* [98] identified approximately one third of their group as cortisol "responders;" sampling over time showed that cortisol levels increased early-on, suggesting that anticipation of stress played a significant role in the observed memory deficits in this subgroup. Twelve-hour urinary-free cortisol excretion has been negatively associated with memory performance in healthy older women, but not men [99]. Longitudinal studies of healthy older adults have shown that increases in cortisol levels over a period of years is associated with cognitive impairment and decline in memory [99,100]. Lupien *et al.* [100] found that the slope of the change in plasma cortisol levels over a period of up to 4 years was correlated negatively with cognitive functioning. The patients who showed an increase in cortisol levels and had a high basal level in the final year were impaired on measures of verbal paired-associate learning and selective attention (visual search task), but not on measures of memory from the WMS or on tests of divided attention or naming. A 1-year follow-up study also demonstrated an impairment in vigilance in those patients with increasing cortisol levels who did not develop the same degree of hypersecretion [101]. Furthermore, prolonged cortisol elevations predicted hippocampal atrophy [92]. Seeman *et al.* [99] similarly found that increases in the level of urinary cortisol excretion over a period of almost 2.5 years was associated with actual declines in memory performance in women (but not men), although there were no effects on measures of abstraction and visuoconstruction. In a recent study, Lupien *et al.* [102] demonstrated some of the complexity in relating cortisol levels with cognitive impairment. Pharmacologic manipulation of glucocorticoids had different effects on memory function depending on a patient's cortisol history. Inhibition of cortisol secretion with administration of metyrapone impaired memory in those patients with a history of moderate cortisol levels; the deficit was reversed after hydrocortisone replacement. In contrast, metyrapone did not effect memory in those with a history of high cortisol levels and current memory deficits, but hydrocortisone treatment significantly decreased delayed memory. Memory problems associated with repeated stress and HPA axis dysregulation may be specifically mediated by glutamate's neurotoxic effect on the hippocampus. For example, Alvarez and Banzan [103] have shown that chemical stimulation of ventral hippocampus glutamate receptors inhibit learning and memory in adult rats. A metabotropic glutamate receptor antagonist can reverse the learning deficit.

The finding of Lupien *et al.* [98] that memory impairment was associated with early cortisol elevations corresponding to the anticipation of stress is particularly important for understanding the role of stress in the cognitive functioning of patients with chronic pain. The belief that pain symptoms are inevitable is a core feature of the chronic pain syndrome for many patients. The anticipation of pain is a significant psychologic stressor that may be associated with dysregulation of the HPA axis. Furthermore, the anticipation of pain has been associated with modified activity at ACC regions that play a role in effortful information processing [56] and at ACC regions that have been implicated in anxiety and stress reactions [2•]. Therefore, the anticipation of pain may disrupt information processing and the allocation of attentional resources through neuronal activity at the ACC. A recent study showed that anticipation of an impending and unpredictable pain stimulus increased rCBF in the caudal portion of the ACC and anticipation of an inevitable, but predictable pain stimulus resulted in a decrease of rCBF [104]. Subjects in this study reported promptly attending to or intentionally distracting their attention from pain. To the extent that aspects of chronic clinical pain are difficult to predict, this observation raises the possibility that a patient may become increasingly vigilant, emotionally aroused, and somatically focused, which could have the effect of reducing the capacity for effortful cognitive processing.

The negative effect of HPA axis dysregulation on cognitive function is consistent with the idea that the concomitants of chronic pain (*eg,* emotional distress) are related to neuropsychologic deficits. It is plausible that the patterns of HPA axis dysregulation in chronic pain represent variants of the periodic HPA and the autonomic and neurochemical reactivity that McEwen [87] postulates may underlie progressive neuronal changes. There is evidence from longitudinal studies [99] that a decline in cortisol levels may be associated with an improvement in cognition. Effective treatment of chronic pain symptoms may minimize repeated HPA axis activation, reduce cognitive inefficiency as a result of associated distress, and partially reverse any stress-related changes in brain structure or function.

Conclusions

The studies that have been reviewed suggest an association between psychologic distress and cognitive impairment in patients with chronic pain. In particular, pain-related negative emotions and variables that mediate suffering (*eg*, interference with activities and increased somatic vigilance) have been identified in a number of studies as correlates of cognitive impairment. Studies employing multiple regression analysis or structural equation modeling have extended earlier findings that suggested that psychologic distress is related to cognitive impairment independent of the effects of pain intensity. However, beyond this general distinction between sensory-discriminative and later stages of pain processing, research has not systematically and comprehensively explored the interrelationships among the numerous variables that potentially mediate the association between psychologic distress and cognitive impairment.

The ACC appears to be play an important role in pain processing, especially with regards to the affective-motivational dimension of the experience. As an area of the brain that modulates emotional reactivity and contributes to an executive attentional system, it may be an integral component of the neural system that mediates the impact of pain-related emotional distress on cognitive functioning, including the allocation of attentional resources. Mechanisms related to competitive demand on resources, interference effects, or reciprocal suppression between the affective and cognitive subdivisions of the ACC may underlie the disruption of cognitive function. Maladaptive physiologic stress responses and dysregulation of the HPA axis is another plausible cause of cognitive impairment in patients with chronic pain, including memory deficits secondary to effects on hippocampal function. Physiologic responses to repeated stress have been related putatively to changes in brain structure and function. A particularly intriguing possibility is that the anticipation of pain symptoms that are difficult to predict, especially in those patients who are high in trait neuroticism, is a significant stressor that repeatedly activates the HPA axis and ACC areas, resulting in cognitive impairment.

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