Somatoform Pain: A Developmental Theory and Translational Research Review

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Somatoform pain is a highly prevalent, debilitating condition and a tremendous public health problem. Effective treatments for somatoform pain are urgently needed. The etiology of this condition is, however, still unknown. On the basis of a review of recent basic and clinical research, we propose one potential mechanism of symptom formation in somatoform pain and a developmental theory of its pathogenesis. Emerging evidence from animal and human studies in developmental neurobiology, cognitive-affective neuroscience, psychoneuroimmunology, genetics, and epigenetics, as well as that from clinical and treatment studies on somatoform pain, points to the existence of a shared neural system that underlies physical and social pain. Research findings also show that nonoptimal early experiences interact with genetic predispositions to influence the development of this shared system and the ability to regulate it effectively. Interpersonal affect regulation between infant and caregiver is crucial for the optimal development of these brain circuits. The aberrant development of this shared neural system during infancy, childhood, and adolescence may therefore ultimately lead to an increased sensitivity to physical and social pain and to problems with their regulation in adulthood. The authors critically review translational research findings that support this theory and discuss its clinical and research implications. Specifically, the proposed theory and research review suggest that psychotherapeutic and/or pharmacological interventions that foster the development of affect regulation capacities in an interpersonal context will also serve to more effectively modulate aberrantly activated neural pain circuits and thus be of particular benefit for the treatment of somatoform pain. **Key words:** somatoform pain, pain disorder, somatization, developmental neuroscience, interpersonal affect regulation, interpersonal distress.

SP = somatoform pain; **SSD** = somatization spectrum disorder; **ACC** = anterior cingulate cortex; **PFC** = prefrontal cortex; **fMRI** = functional magnetic resonance imaging; ***OPRM1*** = μ-opioid receptor 1 gene.

INTRODUCTION

Somatoform pain (SP) is one of the primary symptoms of somatization spectrum disorders (SSDs) (1), which are characterized as "a tendency to experience and communicate somatic distress in response to psychosocial stress." These disorders are highly prevalent, debilitating, and challenging to treat. Prevalence rates of SSD vary depending on the number of medically unexplained symptoms included in the diagnosis, reaching up to 17% in the general population and accounting for nearly 25% of all visits to primary care clinics (1–5). SSD leads to high levels of disability (6) and excessive and ineffective use of health care (7). SSD costs an estimated $256 billion annually in the United States, an amount nearly double the annual $132 billion cost of diabetes (8). Extant treatments are only moderately effective and/or not well validated. The quest for development of effective treatments and prevention would be most efficient if it were based on a comprehensive understanding of the causes of this condition. Its etiology, however, is still unknown. The purpose of this review was to present a developmental theory of the pathogenesis of SP based on an integration of research findings from clinical and basic sciences.

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The nosology of SP is complex and evolving, reflecting a continuous debate on the diagnostic classification of SSDs in general. In DSM-IV, three disorders include SP: somatization disorder, pain disorder, and undifferentiated somatoform disorder. This classification is, however, widely challenged (9–12) and, in the DSM-V proposal, SP would move into a new, more comprehensive diagnostic category, "complex somatic symptom disorder," with the subtype modifier "with predominant pain." SP is also the most common symptom in the research categories of abridged somatoform disorder, multisomatoform disorder, and medically unexplained symptoms (9,10). In nonpsychiatric medical offices, many patients with SP are diagnosed as having "functional syndromes" (e.g., irritable bowel syndrome, fibromyalgia). SP may overlap significantly with these functional syndromes because both include pain symptoms. However, unlike SP, these syndromes do not require the criterion that "psychological factors play a major role in the onset or maintenance of pain." Therefore, a subgroup of patients with functional syndromes may experience SP. Because the focus of this review is SP, we will only review studies of functional syndromes (e.g., fibromyalgia) that address psychological factors, therefore making those studies specifically relevant to SP. SP can also exacerbate an existing medical condition or be comorbid with other psychiatric disorders (e.g., depression, anxiety, and hypochondriasis). The validity of different diagnostic nosologies for SSDs is, however, beyond the scope of this review. We focus specifically on SP and the potential mechanism of formation of this symptom.

DEVELOPMENTAL THEORY OF SOMATOFORM PAIN

Several basic assumptions are at the foundation of this proposed developmental theory. First, Cartesian mind-body dualism is replaced by a postulation that "mind" and "body" are not distinct entities but rather different levels of inquiry about the human condition. Going beyond the notion of "mind-body connection," we assume that a) any psychological process is biological (e.g., the subjective feeling of being in love involves changes in the brain and body) and b) any biological process is

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experienced by a person subjectively, with or without that person's conscious awareness, and can be influenced by this subjective experience (e.g., a patient with depression may have longer recovery after routine surgery because of an altered postsurgical immune response modulated by the patient's depressed state). It is by the integration of multiple levels of inquiry that a more comprehensive understanding of the etiology of a clinical problem is established (13). Second, somatization is not, in itself, a disorder. Rather, it is one of many natural ways that people experience and communicate distress. Moreover, somatization is a developmentally appropriate response to stress in infants and children, which diminishes with age as more mature capacities for distress and affect regulation are developed. The extent to which somatic reactions become chronic and distressing varies on a continuum. In this review we focus on somatic reactions to stress that become overwhelming or severely impair a person's functioning, warranting clinical intervention. Third, the same presenting symptoms can have various etiological mechanisms; therefore, the proposed theory may be applicable to some, but not all, manifestations of SP.

The essence of this developmental theory of SP is that suboptimal early interpersonal experiences with caregivers may interact with one's genetic predisposition, leading to a disrupted maturation of neural circuits involved in affect regulation and interpersonal functioning, yielding the persistence into adulthood of developmentally earlier tendencies to experience distress somatically. Recent research has shown that affects associated with interpersonal distress and attachment share neurological substrates with somatic pain (14). Therefore, the interplay of adverse early experiences and genetic predisposition may influence the development of this shared neural system, resulting in increased susceptibility to SP in adulthood due to the altered neural dynamics of somatic distress, interpersonal distress, and affect regulation (Fig. 1).

In prenatal and early postnatal life, distress and excitement are experienced primarily somatically since higher-order affect regulation and cognition are not yet developed. The mother (or primary caregiver) reduces the infant's distress by attending to the infant's needs, either eliminating the source of distress (e.g., feeding) or helping the infant regulate the distress (e.g., holding and caressing an infant whose stomach hurts). The distress at this stage of development is regulated primarily via interpersonal interactions. These early interactions lay the foundation for the ways in which the infant will regulate one's own distress in the future.

During optimal early infant development, the mother/caregiver is sensitively attuned to the infant's physical and emotional needs. As the infant develops, the mother gradually increases separation, allowing the maturing infant to learn to regulate one's own distress while providing the needed care so that the infant is not overwhelmed with unmet needs or excessive stimulation. The infant's affective reactions gradually

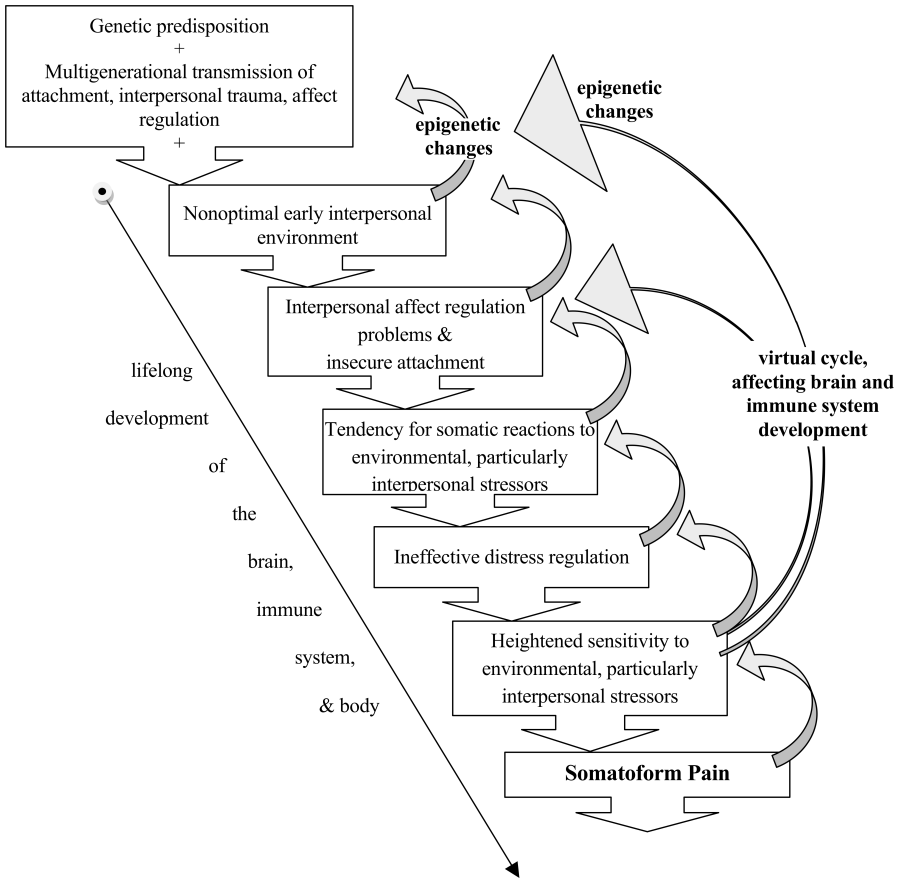

Figure 1. Developmental theory of somatoform pain.

evolve from primarily somatic to more complex experiences of emotion and their regulation, including learning cross-modal symbolization of affect (e.g., responding to a soothing song), developing an internal representation of the caregiver (e.g., a memory of mom when she is not in sight), developing a notion of object constancy (e.g., anticipation that the caregiver will attend to the infant's needs), using a toy or a transitional object for comfort (e.g., "security blanket"), and, later in development, expressing feelings in words, play, or fantasy and making more appropriate attributions regarding inner emotional states. Caregivers support these growing capacities in the infant in various ways, including the sharing and mirroring of affect, which contribute to the development of representations of self and other—the building blocks of affect regulatory capacities.

However, if the infant is overwhelmed by unmet needs or excessive stimulation, if the caregiver does not effectively help the infant learn to regulate one's affect, or if constitutional predispositions interfere with the learning of self-regulatory strategies, the child may continue to experience and express emotional distress somatically. Similarly, overprotection or problems with proper caregiver-infant separation (e.g., resulting from the caregiver's own needs for closeness or dependency) may compromise the development of the infant's capacities to self-regulate affect.

Moreover, parent-child interaction is a mutually regulated system. Unable to express emotions to others in a nonsomatic way (through play, gestures, or linguistic expression of affect), a child may often fail to elicit emotional support, attention, and understanding from caregivers, which support the further development of more mature ways of self-regulating emotional distress. Absence of the desired response from others, in turn, may be perceived by the child as evidence that others are not able to respond in the desired way and/or do not sufficiently care about him or her, which may diminish the child's openness to expressing affect, thus creating a vicious cycle of unexpressed and unregulated affect, increased emotional distress, increased likelihood of somatic expression of that distress, and further emotional withdrawal of caregivers, all leading to an even greater emotional distress in the child—a learning experience that inevitably leads the child to be less and less likely to express emotions in nonsomatic ways.

These compromised interpersonal interactions are usually not isolated events but ongoing characteristics of a child's environment, affecting the development of brain circuits, immune system, and other bodily systems (Fig. 1). Difficulties in coping with interpersonal stressors in infancy, childhood, and adolescence therefore likely alter brain development (15,16) and may perpetuate and accentuate the tendency to experience emotional distress somatically. As adults, people with predominantly somatic ways of expressing distress may have problems establishing and maintaining relationships, further exacerbating interpersonal affect regulation problems, poor social support, and loneliness. Ironically, patients with SP often seek help for somatic symptoms from their medical doctors, who are unable to provide pain relief using current medical treatments. Often, doctors' failure to help is perceived by patients with SP as yet another interpersonal rejection, further perpetuating the cycle of distress and pain. This theory of pathogenesis and symptom formation suggests that treatment of SP should focus on helping patients develop more mature ways of regulating affect within an interpersonal environment. The developmental origins of SP have been suggested by many clinicians (17). In this review, we present recent translational research findings that provide evidence in support of this theory and offer a neurocircuitry-based understanding of one of the potential mechanisms of symptom formation in SP.

MULTIDISCIPLINARY RESEARCH FINDINGS

Clinical Research

Evidence from clinical research suggests that patients with SP tend to have a high prevalence of insecure attachment, interpersonal problems, and affect regulation difficulties; that many of them grow up in a nonoptimal interpersonal environment; and that their somatic symptoms are often activated and maintained by interpersonal distress.

Early Childhood Experiences

A history of nonoptimal early childhood care or trauma is common among patients with SSD: early childhood caregivers of patients with SSD were reported to be unavailable or to have provided less maternal care (18), were more likely to have long-term disability (19), or were more likely to be more punitive and rejecting (20) than caregivers of control participants. Patients with SP and fibromyalgia report more sexual and physical abuse, emotional misattunement, lack of physical affection, separations, and substance abuse in parents than patients with medically explained pain (21). Inpatients with SSD reported high rates of loss of a parent or a caretaker before the age of 17 years (22). Outpatients with SSD had more stress factors associated with changes in interpersonal relationships and the death or disease of close relatives compared with patients without SSD (23). In a study of 515 traumatized people, those who survived interpersonal traumas (e.g., loss or abuse) had significantly more somatic symptoms than victims of disasters (e.g., earthquake or fire) (24). Recent studies suggest that parental style (e.g., rejection, hostility, emotional unavailability) rather than abuse per se is associated with SSD (25,26).

Affect Regulation

SSDs are conceptualized by many as a disorder of affect regulation largely related to patients' marked difficulties with awareness and expression of emotions (27). A strong association between somatization and alexithymia was reported in numerous studies of both clinical and nonclinical populations (28,29) and among patients with SP specifically (30–32).

Alexithymia, in turn, is strongly associated with interpersonal difficulties, insecure attachment, and problems trusting others (33–36). A longitudinal study of 42 infants using the "strange situation paradigm" (an observational method to assess attachment in infancy) showed that insecurely attached infants were more likely to have a failure or significant delay in

the acquisition of verbal expression of internal states and verbal expression of emotions later in childhood (37). Among 149 inpatients, patients with alexithymia presented with a more avoidant social interaction style and more insecure attachment than did patients without alexithymia (38). In nonclinical samples, alexithymia was associated with a fearful and preoccupied attachment style and with the number of reported somatic symptoms (39) and with mistrust, discomfort with closeness, and need for acceptance by others (36). Alexithymia is also associated with a history of interpersonal trauma, such as a history of childhood emotional, physical, and sexual abuse (40), or a history of maternal abuse and paternal indifference (34) among patients with chronic pain syndromes. In a sample of 3733 children, SP was strongly associated with affect regulation–related psychopathology (e.g., depression or anxiety) (41).

Deficits in mentalization (or theory-of-mind functioning) may also contribute to problems regulating one's own affect and interpersonal relationships. Results of a recent study among inpatients with psychiatric conditions, which evaluated both deficits in emotional awareness in an interpersonal context and deficits in mentalization, suggested that measures of the levels of emotional awareness (assessed from blindly rated patient narratives), combined with measures of theory-of-mind functioning, allow for a correct diagnostic classification of 80% of patients with SSD (42).

Attachment and Interpersonal Functioning in Somatoform Pain

A review of human and animal research from 1966 to 2000 on the association of attachment and interpersonal problems with somatic distress or disease suggested that insecure attachment contributes to a maladaptive regulation of stress and affect, which in turn leads to somatic expression of the distress (43). In addition, in several large studies of patients in primary care, preoccupied and fearful attachment styles were significantly positively correlated with increased reporting of somatic symptoms (44), and patients with medically unexplained symptoms were significantly more likely to have insecure attachment than were participants with medically explained symptoms (45). In a community sample of 1997 adults, anxious attachment style (especially distrust and a fear of loss) was associated with the highest levels of reported somatic symptoms (46). Similarly, in a community sample of 101 couples, insecure attachment style and childhood traumas were strongly associated with somatization (47). Insecure attachment style may actually exacerbate somatization in that patients who anticipate that other people will be rejecting and hurtful may eventually elicit such behavior from others, which in turn confirms fears of rejection and perpetuates the vicious cycle (48).

Well-validated interviews and observer-rated measures that bypass the limitations inherent in self-report instruments provide important evidence for these observations. For example, the Adult Attachment Interview revealed a higher prevalence of insecure attachment in patients with SSD compared with healthy controls (49). Especially important for the developmental theory proposed here are the results of a longitudinal study of 87 children observed between the ages of 11 months and 9 years, which show that attachment style (assessed using the Strange Situation paradigm at 15 months of age) was a strong predictor of somatic complaints such as headaches, stomachaches, and eating problems in middle childhood (50). Attachment representations assessed using blind scorings of the Rorschach Test revealed predominantly an avoidant interaction pattern in 85% of patients with somatoform disorder compared with 1% of patients with psychosis; this avoidant interaction pattern is characteristic of people who recall their parents as rejecting their affective expressions of a desire for closeness (51). A study of the internal representations of relationships revealed that 90% of patients with SP compared with only 10% of healthy controls had an unfulfilled desire for interpersonal closeness combined with a fear of being rejected, hurt, or abandoned as their primary representation of relationships (32). Of particular note is a longitudinal study of patients with SSD showing that their somatic distress correlated highly with weekly exacerbations of relational problems (52). A study of 127 patients in primary care with medically unexplained symptoms and their significant others demonstrated an association between interpersonal context and somatic distress (53).

Developmental Neuroscience: Animal Models

Human studies suggest a link between disruptions in early caretaking and the development of insecure attachment and SP. Animal studies provide the opportunity to test these hypotheses directly by experimentally manipulating early life experiences to evaluate their effects on later development (54). Beginning with the studies done by Harlow (55), which demonstrated interactions with a caregiver (and not just protection and nutrient supply) are essential for the survival of an infant monkey, numerous animal studies have confirmed that disruptions in early care lead to physiological changes that affect subsequent development (14,56–58).

Of particular relevance to the developmental theory of SP are studies demonstrating that early maternal separation in rats changes nociception and analgesia (59–61); decreases the number of brain opioid receptors (61); reduces opioid effects during pain (62); increases susceptibility to infection (63), stress-related gastric ulcers (64), and high blood pressure (65); increases reactivity to stress (66,67); reduces γ-aminobutyric acid type A receptor levels in the medial prefrontal cortex (PFC) and in noradrenergic cell body regions of the locus coeruleus and the nucleus tractus solitarius (68); and decreases growth hormone factor (69). Studies show that maternal separation causes acute changes in an infant rat's physiology and behavior, which are not simply expressions of an infant's stress response but rather reflect the loss of specific physiological and behavioral mother-infant regulatory interactions. Subsequent research on these "maternal regulators" revealed an extended system linking the brain, autonomic, and endocrine pathways, as well as behavioral and sleep-wake state organization, including specific thermal, nutrient, and sensory-motor interactions between mother and pup (54,58). Other animal studies have also linked naturally occurring poor maternal care (70) or experimentally

simulated early abuse (e.g., by associating maternal care with shock) with aberrant neural development (71). The discovery of these maternal regulatory interactions provided a new understanding of how different patterns and qualities of maternal interaction shape the course of infant development, including effects on the neural substrates underlying pain and interpersonal distress.

Moreover, animal models point specifically to the existence of a shared neural system involved in the regulation of somatic pain and social distress. The opioid system, for example, plays a role in both analgesia and reaction to social separation. The administration of opioids decreases separation cries among dog pups (72), rat pups (73), and nonhuman primates (74). Oxytocin is also involved in nociception, affiliative behaviors, mating, and caregiver-infant attachment (75–77). The anterior cingulate cortex (ACC), which is involved in the processing of somatic pain, is also involved in the production of separation vocalizations and the maintenance of affiliative behaviors in animals (14,56). Thus, animal research supports the hypothesis that somatic pain and early attachment share neural systems and that the development of these systems can be compromised by nonoptimal maternal-infant regulation.

Cognitive-Affective Neuroscience

Cognitive-affective neuroscience also suggests that a shared neural system is involved in the processing of both physical pain and interpersonal distress. Functional magnetic resonance imaging (fMRI) studies show that the neural circuits involved in the processing of physical pain (e.g., ACC, insula) also process experimentally induced feelings of social rejection (14,78–83). (This involvement is specific for feelings of interpersonal distress versus negative emotions in general (81).) The PFC was shown to down-regulate the distress associated with both pain and social exclusion (80,81). In an experimental study of this shared neural system among participants who reported higher levels of rejection sensitivity in their daily lives, pain threshold decreased disproportionately after an experience of experimentally induced feelings of social rejection (84). Administration of acetaminophen both reduces subjective feelings of social rejection and alters the activation of ACC and insula during social exclusion, further supporting the existence of a shared neural system for social and somatic distress (85).

Patients with SP (86), chronic low back pain (87), and fibromyalgia (88) have a hypersensitivity to experimentally induced pain and augmented central processing of pain in affective-motivational nociceptive circuits (ACC and insula) and in areas known to modulate affect (medial PFC), as demonstrated by fMRI studies (86–90). Single-photon emission computed tomography of patients with SP revealed regional cerebral blood flow alterations consistent with those findings (91). Future research should evaluate whether, in addition to the aberrantly activated affective pain neural circuits, the extent of sensory pain neurocircuitry activation helps define clinically distinct subgroups of patients. The same affective pain–modulating regions were also linked to alexithymia in a positron emission tomography study (92) and to emotional awareness in an fMRI study (93). A structural MRI study demonstrated that the size of ACC inversely correlates with alexithymia (94).

μ-Opioid receptors mediate both attachment behaviors (95) and pain perception (79), thus providing further evidence of a shared pain–interpersonal distress neural system. Variations in μ-opioid receptor 1 gene (*OPRM1*) were associated with sensitivity to social rejection and with activation of ACC in response to experimentally induced feelings of social rejection in fMRI (96). Reduced μ-opioid receptor binding potential was demonstrated by a positron emission tomography study of patients with fibromyalgia (97). Consistent with the findings of problems with emotional awareness in SP, a defensive-repressive coping style was shown to correlate with pain sensitivity, and this relationship was mediated by altered activity of the endogenous opioid system (98). Evidence that oxytocin plays a role in nociception, as well as in attachment, interpersonal trust, and social cognition, provides further support for a shared interpersonal affect regulation–pain system (77,99).

Genetics and Epigenetics

Genetic Predisposition

Potential mechanisms of genetic predisposition to SP include polymorphisms that influence the following: a) sensitivity to pain; b) sensitivity and reactivity to interpersonal stress, predisposing to insecure attachment; and c) affect expression and regulation capacities. Genes that code for proteins in the opioid system (such as *OPRM1*) are implicated in both the processing of somatic pain and the formation of social attachments (95,100). Polymorphisms in the μ-opioid receptor gene, δ-opioid receptor subtype 1 gene, and catechol-*O*-methyltransferase gene were all associated with increased sensitivity to experimentally induced pain (101,102). Mice lacking μ-opioid receptor genes exhibited less attachment-related behaviors such as separation vocalizations and reactions to maternal cues (95). Consistent with these findings, the expression of *OPRM1* in patients with fibromyalgia positively correlates with the severity of pain symptoms (103). In addition, genetic factors may predispose a child to be sensitive to particular types of parental interaction (104). For example, dopamine *DRD4* gene variations have been reported to differentially interact with maternal attachment style (105) and parenting quality (106) to predict the attachment styles and interpersonal behaviors of human infants.

Epigenetic Influences

Multiple studies show that the early life environment influences gene expression and regulation. Disruptions and/or insufficiency of maternal care affects gene methylation patterns, thus altering gene expression in brain cells and leading ultimately to changes in attachment and altered development (58). These epigenetic changes can be transmitted to the next generation but are reversed if offspring are placed in an enriched environment (70). Organisms are particularly susceptible to such epigenetic changes early in life because neurophysiologic pathways for multiple regulatory processes are established at that time.

Psychoneuroimmunology

Environmental influences on the developing immune system can have lasting consequences, affecting a person's illness vulnerability and health resiliency throughout life (107). Frequent exposure to "danger signals" early in development might stimulate immune responses and lead to overproduction of proinflammatory cytokines by the brain and sensitization of the immune system to danger (108). From an evolutionary perspective, feeling alone or feeling rejected by others may be a danger signal for an infant who would not be able to survive without others (14). In fact, isolation is often used in animal models of the effects of stress on development. This research shows that isolation may lead to altered cytokine levels peripherally and in the brain, which in turn increase susceptibility to sickness behavior, infections, pain sensitivity, and allodynia after injury (109–112). Interestingly, administration of oxytocin—a neuropeptide associated with social bonding—to isolated rats reversed this effect, reducing the level of the inflammatory cytokine interleukin 1 (IL-1) (111). Consistent with the interpersonal regulation–immunology link, increased social rejection sensitivity as measured by fMRI was associated with an inflammatory response to social stressors (113).

Challenges to the immune system early in development may also lead to sensitization to somatic pain: for example, neonatal activation of the immune system by exposure of rat pups to lipopolysaccharide resulted in heightened nociception to both thermal and mechanical stimulations in adulthood (114). Studies of immune markers in humans with SSD are limited in scope and have produced conflicting results (115). One study, however, showed elevated levels of IL-6, IL-10, and Immunoglobulin E in patients with SSD compared with healthy controls, as well as an inverse relationship between IL-2 and alexithymia; the authors interpreted these findings as supporting activated T helper 2 and reduced T helper 1 pathways among patients with SSD and high level of alexithymia (116). More basic and clinical research is needed to explore the effects of early relational stressors on the development of the immune system and SP.

Treatment Studies

Psychopharmacology

Medication treatment studies of SP without comorbid disorders have been rare, and more studies are needed to illuminate the role of neurotransmitter systems in SP regulation. For example, a meta-analysis of 11 antidepressant treatment studies of SP (with or without depression) revealed variable improvement in pain symptoms (117,118). Two studies have suggested that improvement in SP may be more effectively mediated by agents that affect serotonergic rather than noradrenergic function: one such study used amitriptyline with or without flupentixol (119), and the other compared citalopram versus reboxetine (120).

Psychotherapy

Numerous studies provide evidence that psychotherapy helps to alleviate pain and improve quality of life in patients with SP (117,121–123). Although an in-depth discussion of the relative efficacy of various therapeutic approaches is beyond the scope of this review, this body of research supports the developmental theory of SP proposed here by demonstrating that the experience of pain can be changed by a process of consistent work on affect, cognition, and behavior conducted in a supportive interpersonal environment (124). Studies that explored mechanisms of change in SP suggest that a focus on affect regulation in the interpersonal context contributes to pain symptom improvement. One of the studies most relevant to this review is that of 40 patients with SP randomized to psychotherapy focused on affect and interpersonal relationships or to treatment as usual (125). The pain was reduced significantly more in the psychotherapy group both immediately after treatment and at 1-year follow-up. In fact, 50% of the patients in the therapy group reported complete alleviation of pain after the treatment compared with 15% of controls (125). Most importantly for this review, the study explored the mechanism of change and showed that, after treatment, the patients' awareness of emotions and ability to express affect in the interpersonal context differentially increased whereas the tendency to express interpersonal stress in somatic terms significantly decreased. This change was observed in the active treatment group but not in the control group. In another study, an increase in emotional awareness after inpatient treatment was associated with post-treatment improvement in SSD symptoms, including SP, once again highlighting the relevance of affect awareness and regulation to treatment of SP (126). More studies on mechanisms of change, as well as comparative psychotherapy studies, are needed. In sum, emerging evidence suggests that psychotherapy is helpful for SP. Furthermore, the focus on affect regulation and interpersonal functioning in psychotherapy treatment might be particularly beneficial for patients with SP.

DISCUSSION

This translational integration of research findings supports the developmental theory of SP (Table 1; Fig. 1). Genetic predispositions that affect attachment, affect regulation, and pain processing may all interact with poor caregiver-infant attunement to compromise the maturation of the interpersonal regulation of affect and somatic distress. Failure of these regulatory capacities to develop adequately may contribute to the persistence into adulthood of the primarily somatic way of experiencing emotional distress. This is supported by multiple studies showing that patients with SP tend to have less mature levels of emotional awareness and regulation. Animal models also demonstrate how compromised early interactions with caregivers lead to an increased susceptibility to disease, somatic distress, and altered immune regulation in offspring; human studies are beginning to support this finding.

Moreover, multiple human and animal neuroscience studies demonstrate that interpersonal distress and the experience of somatic pain are mediated by common neural systems (brain neurocircuitry, as well as the neuroendocrine and neuroimmune systems). Therefore, compromised development of these shared systems may lead to an increase in both somatic and interpersonal

TABLE 1. Summary of the Risk Factors, Proximate Causes, and Treatments for Somatoform Pain, Suggested by Current Research

	Levels of Analysis				
	Genes	Molecules and Cells	Neural circuits	Physiology	Behavior and Clinical Phenomenology
Risk factors[a]	Genetic polymorphisms that influence the following: sensitivity to pain, sensitivity and reactivity to interpersonal stress, affect expression and regulation capacities, and/or attachment style Epigenetic influences of non-optimal early interpersonal environment	Low levels of opioids Low levels of oxytocin Dysregulation of cytokines production Dysregulation of Th2 and Th1 cells	Compromised development of neural circuits that are involved in pain and interpersonal distress processing (e.g., ACC, Insula) Compromised development of regulatory circuits (PFC) Decreased connectivity between distress sensitive (ACC, Insula) and regulatory brain regions (PFC)	Increased sensitivity to pain stimuli Compromised development of the immune system	Early interpersonal environment that hinders the maturation of affect regulation capacities (e.g., parental overprotection or emotional unavailability) Interpersonal traumas (e.g. abandonment, disease or loss of a parent)
Proximate causes[b]	Polymorphisms in μ-opioid receptor, d-opioid receptor subtype 1, or catechol-O-methyltransferase genes Epigenetic alterations of gene mythelation patterns that affect development of neural circuits	Decreased availability of the μ-opioid receptors and/or opioids in the brain Depletion of oxytocin Dysregulation of cytokines production Dysregulation of Th2 and Th1 cells	Dysregulation in the shared pain-interpersonal distress neurocircuitry, i.e. hypersensitivity of pain-circuits with exposure to pain or interpersonal distress, and/or poor down-regulation of these circuits by PFC	Heightened sensitivity to pain stimuli and other environmental stressors Increased Inflammatory reactivity (e.g., due to overproduction of proinflamatory cytokines)	Chronic pain Heightened interpersonal sensitivity, difficulty establishing and maintaining relationships Difficulty expressing and regulating affect
Treatment targets and interventions	Early identification of genetic vulnerability and of the poor early interpersonal environment; prenatal identification for the earliest possible intervention Early interventions to improve infant-caregiver interactions in order to prevent epigenetic changes that would adversely affect development and to develop compensatory capacities in case of genetic vulnerability	μ-opioid receptor agonists or antagonists Oxytocin-regulating pharmacologic agents Immune system-regulating agents	Individual psychotherapy, family psychotherapy, and pharmacologic interventions to decrease activation of hypersensitive regions and increase activation of regulatory neural circuits during pain and interpersonal distress	Agents regulating overactive inflammatory response	Individual psychotherapy focused on interpersonal affect regulation, that will lead to decrease in somatic distress Family therapy for child and adult patients focused on development of interpersonal and affect regulation capacities Pharmacotherapy to reduce rejection sensitivity and pain and to strengthen capacities for neural affect regulation

SP = somatoform pain; ACC = anterior cingulate cortex; PFC = prefrontal cortex.

[a] By "risk factors," we mean predisposing factors that increase a person's vulnerability to developing SP symptoms.

[b] By "proximate causes," we mean causes that immediately precede and produce SP symptoms.

distress in childhood and adulthood. This may explain the frequently reported comorbidity of SP, interpersonal difficulties, and problems with interpersonal affect regulation. The symptom formation mechanisms in SP may thus include a) heightened sensitivity to pain and interpersonal interactions, b) problems down-regulating pain and interpersonal distress, or c) a combination of both. In addition, because the experiences of both somatic and interpersonal distress depend on the same shared brain circuits, the tendency to experience interpersonal relationships as rejecting or hurtful may activate somatic pain pathways, and somatic pain may in turn activate pathways involved in feelings of interpersonal rejection. A high frequency of distressing interpersonal interactions throughout life may also contribute to increased pain sensitivity and SP.

The symptom formation mechanisms of SP suggested here are inherently developmental. Multiple research studies point to the association of SP with a history of growing up in an environment suggestive of misattunement between an infant and the caregivers. Therefore, the ongoing vicious cycle of failures in effective distress regulation shapes the developing brain, its neuroendocrine and neuroimmune systems, and their interaction with other body systems. The optimal maturation of these systems depends on learning processes spanning multiple levels, from the psychological level to neurocircuitry development to epigenetics (Table 1).

This compromised developmental process predisposes an adult to increased somatic and interpersonal reactivity and to decreased self-regulatory abilities. Adults with SP continue to experience interpersonal emotional distress at the somatic level. Their interpersonal world is colored by a desire for closeness with others, combined with a fear of rejection and abandonment. This inner representation of relationships makes it difficult for them to engage in interactions that otherwise might help an effective interpersonal regulation of affect, hence perpetuating the cycle of somatic and interpersonal distress. The apparent benefit of psychotherapies that address affect regulation in interpersonal contexts is consistent with the central pathogenic role of interpersonal affect regulation problems in the development of SP.

This developmental theory of SP points to a potential specific mechanism of symptom formation. It is important, however, to acknowledge its limited current specificity. More research is needed to understand particularly what kind of early interpersonal-affective developmental processes may lead to SP or other symptoms in adulthood. The main purpose of the formulation of this theory is to suggest a hypothesis and a direction of research that may further refine or redirect the developmental ideas proposed herein. In addition, this theory suggests one of the SP symptom formation mechanisms that may be applicable to a subgroup but not to all patients with SP. Future investigation should address the variability in the pathogenesis of SP.

Clinical Implications

The reviewed research findings and the proposed symptom formation mechanism of SP suggest that a tailored psychotherapy approach for SP would address developmental deficits that contribute to maladaptive interpersonal affect regulation in patients with SP. Therapeutic techniques that help the individual learn to modulate interpersonal distress more effectively would be expected to reduce the reactivity of pain-related circuits and to enhance the engagement of prefrontal regions in distress regulation. This can be achieved by psychotherapies that help a patient work through insecure attachment and learn to establish close, safe, and supportive interpersonal connections. With effective treatment that focuses on emotional regulation in the interpersonal context, patients with SP will be able to express emotions to others in more mature ways, yielding more effective interactions that can in turn ameliorate interpersonal affect regulation. Pharmacological treatments that address dysregulation in the somatic-interpersonal neurocircuitry may potentially augment the psychotherapeutic process. Opioid and oxytocin systems may be good initial targets for this approach.

An understanding of SP that is rooted in neurobiology may also help to stop the dismissive and invalidating labeling of SP as "not real," which exacerbates patients' feelings of being misunderstood. It may also help patients to see the connection between their pain and emotional distress and to become more accepting of a referral to psychotherapy.

Another important implication of the theory proposed here is that an awareness of the role of interpersonal dysregulation among patients with SP and its developmental origins may help clinicians regulate their own frustration and feelings of helplessness when working with these patients (127). Moreover, it may help physicians to be more effective in alleviating patients' distress and in facilitating referral to psychotherapists, who would then use techniques that address interpersonal affect dysregulation. Patients with SP are very sensitive to interpersonal interactions and are more likely to perceive clinicians as bored or uninterested, which would reinforce their feelings that "no one cares about them," diminish their trust in clinicians, and lead to more pain, perpetuating a vicious cycle. Clinicians' direct attention to such feelings and attunement to patients' heightened need for a safe interpersonal environment could help break this maladaptive cycle.

The pivotal importance of the patient-doctor relationship in enhancing treatment compliance and improved outcome (including alleviation of pain symptoms) has been demonstrated by prior research (128), and efforts to incorporate these results into medical education programs are underway (129). Our theory would suggest that educational modules focused specifically on enhancing interpersonal encounter and interpersonal affect regulation may be particularly helpful for the clinical care of patients with SP and other SSD symptoms.

The research reviewed here also suggests that early life interventions would be of great importance for preventing and alleviating SP. In particular, interventions focused on caregiver-infant interaction and interpersonal affect regulation could alter the developmental trajectory of SP (outlined in Fig. 1) and help restore a more optimal interpersonal environment for a maturing infant. For example, early parent-level interventions for mothers of socioeconomic disadvantage have been shown to be effective

in improving the health of their children (130,131). A similar approach may be helpful for the prevention of SP. Because of the important contribution of interpersonal functioning to the development of SP, infants, children, and adults with SP may also greatly benefit from family therapy interventions (132).

Implications for Future Research

Translational research is on the verge of revealing the pathogenic mechanisms of SP. Longitudinal studies addressing genetic, immune, and neural systems development; parenting environment; parent-child mutual affect regulation; and interpersonal functioning in the same patients are needed to address the developmental hypotheses proposed in this review. The identification of early markers for SP (whether biomarkers, environmental factors, or psychological markers) could contribute to the prevention and early treatment of SP. It is necessary to develop effective targeted treatments of SP and to study the mechanisms of change. Future research may also identify subgroups of patients for whom targeted psychosocial and pharmacological treatments can be devised.

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