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Somatoform Pain: A developmental theory and translational research review

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Abstract

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 mechanisms of symptom formation in somatoform pain and a developmental theory of its pathogenesis. The emerging evidence from animal and human studies in developmental neurobiology, cognitive-affective neuroscience, psychoneuroimmunology, genetics, epigenetics, and clinical and treatment studies of somatoform pain all point to the existence of a shared physical and social pain neural system. Research findings also show that non-optimal early experiences interact with genetic predispositions to influence the development of this shared system and ability to regulate it in an effective way. 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, therefore, may 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 reviewed research suggest that psychotherapeutic and/or pharmacologic 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 in the treatment of somatoform pain.

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Keywords

Somatoform Pain; Pain Disorder; Somatization; Developmental Neuroscience; Interpersonal Affect Regulation; Translational Research

Introduction

Somatoform Pain (SP) is one of the primary symptoms of somatization spectrum disorders (SSD)(1) - 'a tendency to experience and communicate somatic distress in response to psychosocial stress.' These disorders are highly prevalent, debilitating, and challenging to treat. SSD prevalence rates vary depending on the number of medically unexplained symptoms included in the diagnosis, reaching up to 17% of 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 U.S., an amount nearly double the annual \$132 billion cost of diabetes (8). The 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 is to present a developmental theory of pathogenesis of somatoform pain based on an integration of research findings from clinical and basic sciences.

The nosology of SP is complex and evolving, which reflects continuous debate on diagnostic classification of SSDs in general. In the 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-5 proposal SP would move into a new more comprehensive diagnostic category "Complex Somatic Symptom Disorder," with the subtype modifier "with predominant pain." SP is the most common symptom in the research categories of Abridged Somatoform disorder, Multisomatoform disorder, and Medically Unexplained Symptoms (9, 10). In non-psychiatric medical offices many SP patients are diagnosed with "functional syndromes" (e.g. Irritable Bowel Syndrome, Fibromyalgia). SP may overlap significantly with these functional syndromes as 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 suffer from 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 for 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. Herein we focus specifically on somatoform pain 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 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 a routine surgery due to an altered post-surgical 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 itself a disorder. Rather, it is one of many natural ways people experience and communicate distress. Moreover, somatization is a developmentally appropriate response to stress in infants and children that diminishes with maturation 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. Herein 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 somatoform pain.

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 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 experience and a genetic predisposition may influence the development of this shared neural system, resulting in increased susceptibility to SP in adulthood due to altered neural dynamics of somatic distress, interpersonal distress, and affect regulation (Figure 1).

In prenatal and early postnatal life, distress and excitement are experienced primarily somatically, as 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 a baby 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 its distress in the future.

During optimal early infant development, the mother/caregiver is sensitively attuned to the baby's physical and emotional needs. As the infant develops, its mother gradually increases the separation, allowing the maturing infant to learn to regulate its 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 evolve from the primarily somatic to more complex experiences of emotion and their regulation, including 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., the anticipation that the caregiver will attend to the baby'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 contributes to the development of self- and other- representations -- 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 its 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., due to caregiver's own needs for closeness or dependency) may compromise the development of the baby's capacities to self-regulate affect.

Moreover, a child-parent interaction is a mutually regulated system. Unable to express emotions to others in a non-somatic way (through play, gestures, or linguistic expression of affect), a child may often fail to elicit emotional support, attention, and understanding from caregivers that support the further development of more mature ways of self-regulating emotional distress. An 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, unregulated affect, increased emotional distress, increased likelihood of somatic expression of that distress, further emotional withdrawal of caregivers, all leading to an even greater emotional distress in the child—a learning experience, which inevitably leads the child to be less and less likely to express emotions in non-somatic ways.

These compromised interpersonal interactions are usually not isolated events, but ongoing characteristics of a child's environment, affecting the development of brain circuits, the immune system, and other bodily systems (Figure 1). Difficulties in coping with interpersonal stressors in infancy, childhood, and adolescence therefore likely alter development of the brain (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, SP patients often seek help for somatic symptoms from their medical doctors, who are unable to provide pain relief using current medical treatments. Often doctor's failure to help is perceived by SP patients 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). Here 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 mechanisms in SP.

Multidisciplinary Research Findings

Clinical Research

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

Early Childhood Experiences—A history of non-optimal early childhood care or trauma is common among SSD patients: early childhood caregivers of SSD patients were reported to be unavailable or providing less maternal care (18), were more likely to have long-term disability (19), or to be more punitive and rejecting (20) than caregivers of control subjects. SP and fibromyalgia patients report more sexual and physical abuse, emotional misattunement, lack of physical affection, separations and substance abuse in parents than medically explained pain patients (21). SSD inpatients reported high rates of loss of a parent or a caretaker before age 17 (22). SSD outpatients had more stress factors associated with changes in interpersonal relationships and the death or disease of close relatives compared to non-SSD patients (23). In a study of 515 traumatized people, those who survived interpersonal traumas (e.g., loss or abuse) had significantly more somatic symptoms than did the victims of disasters (e.g., earthquake or fire) (24). Recent studies suggest that the parental style (e.g., rejection, hostility, emotional unavailability) rather than abuse per se is associated with SSD (25, 26).

Affect Regulation—Somatization is 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, alexithymic patients presented with a more avoidant social interaction style and more insecure attachment than did non-alexithymic patients (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 psychiatric inpatients which examined both deficits of 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 correct diagnostic classification of 80% of SSD patients (42).

Attachment and Interpersonal Functioning in SP—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 maladaptive regulation of stress and affect, which, in turn, leads to somatic expression of the distress (43). Additionally, in several large studies of primary care patients, 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 1,997 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 SSD patients 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, showing 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 somatoform patients compared with 1% of psychotic patients; 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 SP patients 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 SSD patients which showed that their somatic distress correlated highly with weekly

exacerbations of relational problems (52). A study of 127 primary care patients with medically unexplained symptoms and their significant others demonstrated an association between interpersonal context and somatic distress (53).

Developmental Neuroscience-Animal Models

While 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 examine their effects on later development (54). Beginning with Harlow's demonstration that interactions with a caregiver (and not just protection and nutrient supply) are essential for survival of an infant monkey (55), numerous animal studies confirm 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 which demonstrate that early maternal separation in rats changes nociception and analgesia (59-61), decreases the number of brain opioid receptors (61) and reduces opioid effects during pain (62); increases susceptibility to infection (63), to stress-related gastric ulcers (64) and to high blood pressure (65); increases reactivity to stress (66, 67), reduces GABA-A receptor levels in the medial prefrontal cortex 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 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 pain and interpersonal stress neural substrates.

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 the 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 both nociception and affiliative behaviors, mating and infant-caregiver attachment (75-77). The anterior cingulate cortex (ACC), which is involved in the processing of somatic pain, is also involved in animals in the production of separation vocalizations and the maintenance of affiliative behaviors (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 non-optimal 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 to feelings of interpersonal distress vs. negative emotions in general (81)). The prefrontal cortex (PFC) appears 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 activation of the 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, insula), and in areas known to modulate affects (mPFC) as demonstrated by fMRI studies (86-90). Single photon emission computed tomography of SP patients revealed regional cerebral blood flow alterations consistent with those findings (91). Future research should examine 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 are also linked to alexithymia in a Positron Emission Tomography (PET) study (92) and to emotional awareness in a fMRI study (93). A structural MRI study demonstrated that the size of ACC inversely correlates with alexithymia (94).

Mu-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 the μ -opioid receptor gene (OPRM1) were associated with sensitivity to social rejection and with activation of the ACC in response to experimentally induced feelings of social rejection in fMRI (96). Reduced μ -opioid receptor binding potential was demonstrated by a PET 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: a) the 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 fibromyalgia patients 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 affect gene methylation patterns, thus altering the gene expression in brain cells, and leading ultimately to changes in attachment and altered development. 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, as 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, lead to the overproduction of proinflammatory cytokines by the brain, and to sensitization of the immune system to danger (108). From an evolutionary perspective, feeling alone or 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, which show that isolation may lead to altered cytokine levels peripherally and in the brain, which in turn increases the susceptibility to sickness behavior, infections, pain sensitivity and allodynia post 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 IL-1 (111). Supporting 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 in adulthood to both thermal and mechanical stimulations (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 SSD patients compared to healthy controls as well as an inverse relationship between IL-2 and alexithymia; the authors interpret these findings as supporting activated Th2 and reduced Th1 pathways among patients with SSD and high 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 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 vs reboxetine (120)).

Psychotherapy—Numerous studies provide evidence that psychotherapy helps to alleviate pain and improve quality of life of SP patients (117, 121-123). While 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 address mechanisms of change in psychotherapy would be particularly useful and may provide further insight regarding the etiology of SP. However, these studies have been rare. 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 most relevant to this review, is a study of 40 SP patients randomized to an affect- and interpersonal relationships-focused psychotherapy or to treatment as usual (125). The pain was reduced significantly more in the therapy group both immediately post-treatment and at one-year follow-up. In fact, 50% of the patients in the therapy group reported complete alleviation of pain after the treatment compared to 15% of controls (125). Most importantly for this review, the study explored the mechanism of change and showed that, after treatment, the SP patients' awareness of emotions and ability to express affect in the interpersonal context differentially increased while 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 of mechanisms of change as well as comparative psychotherapy studies are needed. In sum, psychotherapy is helpful for SP, and the focus on affect regulation and interpersonal functioning might be particularly beneficial for the SP patients.

Discussion

This translational integration of research findings supports the developmental theory of SP (Table 1, Figure 1). Genetic predispositions that affect attachment, affect regulation and pain processing may all interact with poor mother-infant attunement to compromise the maturation of 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 SP patients 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 the 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 neuroendocrine and neuroimmune systems). Therefore, compromised development of these shared systems may lead to an increase of both somatic and interpersonal 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) a heightened sensitivity to pain and to interpersonal interactions, (b) problems down-regulating pain and interpersonal distress, or (c) a combination of both. Additionally, because the experiences of both somatic and interpersonal distress depend on the same shared brain circuits, the predisposition to experiencing 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 somatoform pain.

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 its caregivers. Therefore, the ongoing vicious cycle of failures in effective distress regulation shape 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.

This compromised developmental process predisposes an adult to increased somatic and interpersonal reactivity as well as to decreased self-regulatory abilities. Adults with SP continue to experience interpersonal emotional distress on 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 is pointing 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 which may further refine or redirect the developmental ideas proposed herein. In addition, this theory is suggesting one of the symptom formation mechanisms of SP that may be applicable to a subgroup but not all patients suffering from somatoform pain. 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 SP patients. 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 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, SP patients will be able to express emotions to others in more mature ways, yielding more effective interactions which can in turn ameliorate interpersonal affect regulation. Pharmacologic treatments that address the dysregulation in the somatic-interpersonal neurocircuitry may potentially augment the psychotherapeutic process. Opioid and oxytocin systems may be good initial targets for this approach.

Understanding of SP as 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 SP patients 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. SP patients are very sensitive to interpersonal interactions and are more likely to perceive a clinician as bored or uninterested, which would reinforce their feelings that “no one cares about them,” diminish their trust in the clinician, and lead to more pain, perpetuating a vicious cycle. Clinicians' direct attention to such feelings and attunement to SP 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 researchers (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 the interpersonal encounter and interpersonal affect regulation may be particularly helpful for the clinical care of patients with somatoform pain and medically unexplained 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 the caregiver-infant interaction and the interpersonal affect regulation could alter the developmental trajectory of SP (outlined in Figure 1), and help restore a more optimal interpersonal environment for a maturing infant. 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. Due to the important contribution of interpersonal functioning to the development of SP, infants, children and adults suffering from 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. To address the developmental hypotheses proposed, longitudinal studies addressing genetic, immune, neural systems development, parenting environment, child-parent mutual affect regulation and interpersonal functioning in the same patients are needed. The identification of early markers for SP (whether biomarkers, environmental factors, or psychological markers) could contribute to early treatment and prevention of SP. It is necessary to develop effective targeted treatments for 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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Acronyms

SP	Somatoform Pain
SSD	somatization spectrum disorders
DSM	Diagnostic and Statistical Manual of Mental Disorders
ACC	anterior cingulate cortex
PFC	prefrontal cortex
fMRI	functional magnetic resonance imaging
OPRM1	μ -opioid receptor 1 gene
PET	Positron Emission Tomography

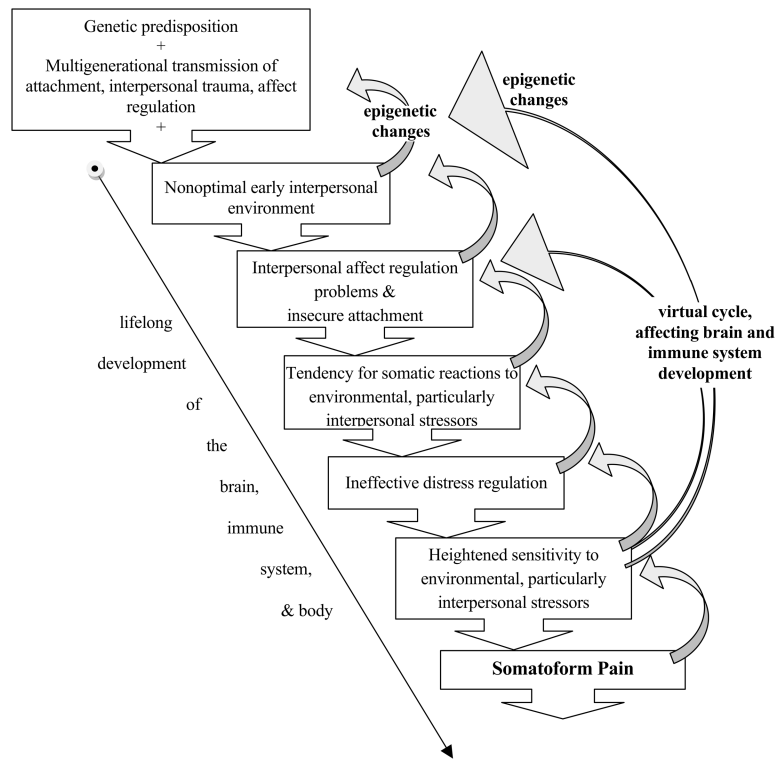


Figure 1.
Developmental theory of somatoform pain.