Commentary: Multiple Pains as Functional Pain Syndromes

Carl L. von Baeyer,1,2 PhD, and G. David Champion,3,4 MD
1Department of Psychology, 2Department of Pediatrics, University of Saskatchewan, 3Department of Anaesthesia and Pain Medicine, Sydney Children’s Hospital and 4School of Women’s and Children’s Health, University of New South Wales

All correspondence concerning this article should be addressed to Carl L. von Baeyer, Department of Psychology, University of Saskatchewan, 9 Campus Drive, Saskatoon, SK S7N 5A5, Canada. E-mail: carl.vonbaeyer@usask.ca

Received November 3, 2010; revisions received December 11, 2010; accepted December 14, 2010

Pain in various parts of the body is reported by many children and adolescents, especially girls. Kroener-Herwig, Gassmann, van Gessel, and Vath (2011, this issue) report on a large community study of youth aged 10–17 years in which 66% of the female respondents and 41% of the males reported pain in two or more body locations within the last 6 months. Headache, abdominal pain, and back pain were the most frequent of these locations. Kroener-Herwig et al. used multiple regression techniques to identify associations as potential predictors of these pains, finding small contributions of psychosocial variables and large contributions of age, sex, and prior pain.

Many interesting questions are raised by the findings of Kroener-Herwig et al., for example: (a) Why do multiple pains often cluster or occur sequentially as they do? (b) What is the basis of the large sex or gender differences in prevalence of pain? (c) Could multiple pains in adolescence predict later chronic pain and psychological illness? We focus in this commentary on the first of these questions. In addressing this question, we briefly survey adult studies related to various functional pain syndromes, finding that they have many shared features and risk factors. We examine twin studies showing shared genetic influences among functional pain syndromes as well as anxiety and depression. We conclude with a portrayal of functional pain syndromes as largely comprising different manifestations of an underlying propensity or vulnerability to respond to stressors with the experience and report of pain, rather than separate disorders. The main constructs discussed in this commentary are summarized in Figure 1.

Why do Multiple Pains often Cluster or Occur Sequentially as they do?

Most research on pediatric pain focuses on pain in individual locations; this is largely a function of the separate interests of various disciplines: neurologists study headache, gastroenterologists study abdominal pain, and so on. Moreover, each of these domains is addressed by separate patient organizations, funding agencies, and divisions within pharmaceutical companies (Mayer & Bushnell, 2009). However, epidemiological studies, including several reviewed by Kroener-Herwig et al., clearly support the conclusion that many or most children and adolescents who have pain experience it in more than one location simultaneously or sequentially over time. Explanations focused on single organ systems cannot account readily for the high prevalence of multiple pains in unrelated systems.

Kroener-Herwig et al. suggest that part of the basis of multiple pains could be a stable trait or biological disposition which they identify as pain vulnerability, a time-honored but under-researched concept. They speculate briefly that a potential mechanism for pain vulnerability could be deficits in antinociceptive systems.

The most prevalent pain disorders of childhood and adolescence are not related to known organic disease or injury, but have in the past been referred to as medically unexplained pain, somatoform or somatization pain disorders, and so on. The terms functional somatic syndromes (Henningsen & Creed, 2010), idiopathic pain disorders (Diatchenko, Nackley, Slade, Fillingim, & Maixner, 2006), and functional pain syndromes (Mayer & Bushnell, 2009) are currently more prominent.
Studies of Functional Pain Syndromes in Adults

There is much to be learned from studies concerning these functional or idiopathic pain syndromes in adults. Characteristic shared features, as reviewed by Diatchenko et al. (2006) and by Mayer and Bushnell (2009), involve individual differences in genetic biological influences, genetic and environmental psychological influences, comorbid interrelationships, and disordered central somatosensory processing including central sensitization of nociception and/or impaired descending inhibitory nociceptive control.

Mayer and Bushnell (2009) reviewed the evidence supporting the specific end-organ model of chronic regional pain syndromes and concluded that the evidence was unlikely to explain these syndromes in the majority of patients. There is an overlap of patient and healthy populations. Most functional pain syndromes, as defined by symptom criteria, show a lack of a distinct boundary between healthy individuals in the general population who have experienced symptoms transiently and the population in which chronic symptoms are present but not severe enough for the person to seek medical care. Like many psychiatric diagnoses, functional pain syndromes “can be viewed as quantitative deviation along continuous trait dimensions that merge imperceptibly from ‘normalcy’ into the ‘pathological’ range” (Mayer & Bushnell, 2009, p. 535). Primary risk factors for functional pain syndromes may relate to individual differences in viscerosomatic sensitivity, peripheral and central sensitization, limbic system responsiveness, or autonomic nervous system activity. Secondary risk factors such as selective attention to bodily sensations, catastrophizing, and symptom-related worries and illness behavior, in addition to psychological stressors, are likely to be shared across all the syndromes. Mayer and Bushnell have proposed a number of explanatory models for the understanding of these functional pain syndromes and to aid further research.

Figure 1. Key constructs discussed in the commentary, showing hypothesized antecedents and consequences of pain vulnerability. Figure copyright ©2010, G.D. Champion and C.L. von Baeyer. Used with permission.
In a population-based twin study (Kato, Sullivan, Evengard, & Pedersen, 2009; Kato, Sullivan, & Pedersen, 2010) the cooccurrence of functional somatic syndromes in women was best explained by affective and sensory components in common to four of the syndromes, as well as by unique influences specific to each of them. Kato et al. interpret their findings as suggesting a complex view of the multifactorial pathogenesis of the illnesses. One of the two latent traits loaded heavily on the psychiatric disorders (major depression and generalized anxiety disorder), whereas the other trait loaded on four of the functional somatic syndromes, particularly chronic widespread pain, but not on the psychiatric disorders. The four illnesses thus identified (chronic widespread pain, chronic fatigue, irritable bowel syndrome, and recurrent headache) were also affected by genetic influences that were specific to each.

Diatchenko et al. (2006) reviewed evidence concerning the influence of psychological distress and of genetic variations on augmentation of the pain experience, and referred specifically to neuroendocrine dysfunction. The idiopathic pain disorders commonly aggregate as “comorbid” conditions that are characterized by complaints of pain as well as a mosaic of abnormalities in motor function, autonomic balance, neuroendocrine function, and sleep. They also show a higher comorbidity than would be expected by chance with anxiety disorders, depression, and posttraumatic stress disorder.

Some of the individual functional pain syndromes, such as migraine, have been shown in twin studies to share genetic influences with anxiety and depression (Ligthart, Nyholt, Penninx, & Boomsma, 2010). A number of genes have now been identified that are associated with both pain sensitivity and psychiatric disorders and that interact with environmental triggers. For example, Maletic and Raison (2009) interpreted the high comorbidity between major depression, fibromyalgia (a prototypical functional pain syndrome), and neuropathic pain as indicating shared biological and environmental underpinnings among the three conditions. From an evolutionary perspective, the authors reflect, it is apparent that both negative emotions and physical pain have a tremendous survival value when current conditions threaten an organism’s goals and/or survival. While the research generally is related to adults, there is no reason to believe that the genetic and environmental relationships between emotional states and pain should not be at least as prominent in children, perhaps more so. Depression and anxiety, and functional pain syndromes such as fibromyalgia “may all be characterised by adaptive processes gone awry as a result of complex interactions between genetic vulnerabilities and environmental factors….” Shared genetic determinants include poorly functional alleles regulating monoaminergic, glutamatergic, neurotrophic, opioid and inflammatory cytokine signaling. Chief among environmental risk factors are psychosocial stress and illness, both of which promote, in vulnerable individuals, relative resistance to glucocorticoids, increased sympathetic/decreased parasympathetic activity, and increased production and release of proinflammatory mediators. Dysregulation of stress/inflammatory pathways promotes alterations in brain circuitry that modulates mood, pain, and the stress response” (Maletic & Raison, 2009). The authors summarized the evidence that these functional changes contribute to central sensitization in pain disorders and “kindling” in depression.

**Pediatric Studies of Functional Pain Syndromes**

Considering the pediatric context, Dunn, Jordan, Mancl, Drangsholt, and Le Resche (2011) conducted a prospective longitudinal study of head, stomach, back, and facial pain in a large sample of adolescents in the community. They identified a cluster or subgroup comprising 12% of adolescents who had persistent pain in at least one site over several time points; this group was predominantly female and had high levels of somatization and depression and low life satisfaction. Their findings were interpreted in terms of a possible lifelong tendency in some individuals to experience pain, either at a specific site, or as a more general tendency to experience pain. Their study contributes to the emerging conceptualization of pain syndromes as different manifestations of an underlying vulnerability rather than separate disorders.

Twin studies have also been done in pediatric populations, almost always focusing on a single type of pain such as migraine. A recent heritability estimate for migraine in twins aged 12–20 years was 30% (Ligthart, van der Aa, Bartels, & Boomsma, 2010). Another study examined widespread pain in 11-year-old twins (Mikkelsson, Kaprio, Salminen, Pulkkinen, & Rose, 2001). Widespread pain was defined as occurring at least once a week, above and below the waist, on both sides of the body, and in the axial skeleton. These authors found greater concordance in females than males for both monozygotic and dizygotic twin pairs. They concluded that genetic factors seem to play a minor role in widespread pain, accounting for at most 10% of total variance. Shared environmental factors unique to each twin pair were considered to be more influential. However, this is in some contrast to studies in adults which have shown more prominent genetic influence in fibromyalgia (Maletic and Raison, 2009).
The linkage of pain vulnerability and of pain in multiple locations with depression has been made in several studies. For example, Little, Williams, Puzanovova, Rudzinski, and Walker (2007) studied 400 children and adolescents with abdominal pain and seven common non-gastrointestinal somatic symptoms (e.g., headaches, chest pain, back pain, tiredness). They found that each addition of a non-gastrointestinal somatic symptom doubled the odds of a positive screen for depression. The optimal cutoff for the classification as depressed was three or more concurrent non-gastrointestinal symptoms.

A Common Biological Susceptibility

In summary, research and theory from diverse sources point to the possibility that multiple pains cluster as they do because they share a common biological susceptibility which is plausibly referred to by Kröner-Herwig et al. (2011) as pain vulnerability and others have referred to as pain sensitivity (e.g., Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley, 2009). That propensity or vulnerability is partly genetically based, including partly shared genetic vulnerability with anxiety and depression, and it is also influenced by environmental factors such as parental modeling and reinforcement, stress, injury, and illness. Additional influences on vulnerability to pain in this context include impairment of pain regulatory systems such as prematurity and early life trauma. They may also include sensory inputs into the central nervous system which may have effects on the location of pain such as somatic tissue injury or inflammation or low-grade somatosensory inputs from repetitive use of the musculoskeletal system (so-called overuse disorders), and repetitive asymptomatic neuropathic inputs from hyperexcitable peripheral nerves. Individuals with high levels of pain vulnerability are likely to be depressed. Pain-vulnerable individuals may also be characterized by hypersensitivity to experimental stimuli and sometimes to non-painful stimuli. Brain imaging studies have typically shown increased neural activation in response to mechanical or thermal experimental pain stimuli and abnormal responses to anticipation of pain.

Further research will be needed to elucidate the genetic, physiological and environmental mechanisms for these phenomena associated with pain vulnerability. The large observed sex or gender differences, in particular, deserve detailed consideration as a way of learning about the mechanisms underlying pain experience and pain modulation. Questions concerning the clinical importance of pain vulnerability in childhood in development of medical and psychological illness in adulthood will require further longitudinal study.

Acknowledgments

The authors acknowledge helpful suggestions provided by Milton Cohen concerning the conceptual model, which was also influenced by the model published by Diatchenko et al. (2006).

Conflicts of interest: None declared.

References


