Annual Research Review: Functional somatic symptoms and associated anxiety and depression – developmental psychopathology in pediatric practice

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Background: Medically unexplained physical symptoms, commonly referred to as functional somatic symptoms (FSS), are common in pediatric medical settings and associated with suffering, impairment, and medical help seeking. The association of pediatric FSS with anxiety and depressive symptoms and disorders across the life span is reviewed. Method: Review and critique of controlled studies examining cross-sectional and longitudinal associations of FSS with anxiety and depressive symptoms and disorders in community-based and clinical samples of children and adolescents. Results: FSS are consistently associated cross-sectionally with anxiety and depressive symptoms and disorders in childhood and adolescence, and the likelihood of associated anxiety and depression increases with the number of reported FSS. The presence of one or more FSS early in life is associated with an increased likelihood of multiple FSS and anxiety and depressive symptoms and disorders later in life, and anxiety and depressive symptoms and disorders in childhood are associated with subsequent multiple FSS. Conclusion: Strong associations between FSS, anxiety, and depression across the life span suggest the need to reconsider existing nosology and reconceptualize symptomatic relationships. Large, population-based longitudinal studies of FSS, anxiety, and depressive symptoms and disorders are needed to establish temporal relationships between the various symptoms and conditions. Keywords: Anxiety, comorbidity, depression, emotion, somatization.

Unexplained symptoms in pediatric practice: conceptual challenges

Primary care is first-contact personal health care that is comprehensive and delivered longitudinally within a community-based medical setting, with the majority of children visiting a primary care physician at least once annually (Costello et al., 1988). Because pediatric psychopathology is common, tends to be chronic, and is associated with significant levels of functional impairment and health risks such as suicide, the recognition and management of psychopathology in primary care is a matter of considerable public health importance. Practical advantages of primary care include ease of access, proximity, familiarity, and relative acceptability to youth and families (Horwitz, Leaf, Leventhal, Forsyth, & Speelhey, 1992). The increasingly popular conceptualization of the medical home refers to a model of team-based primary care delivery that is accessible, comprehensive, continuous, family-centered, and coordinated by a personal physician, with the medical home practice being responsible for directly providing or appropriately arranging care with other qualified professionals for all of the patient's health care needs (American Academy of Pediatrics, Medical Home Initiatives for Children with Special Needs Project Advisory Committee, 2002). Addressing psychopathology in primary care also creates an opportunity to challenge stigma and improve real-world access to services for affected children and families.

Unfortunately, the promise of the primary care setting in the recognition and management of pediatric psychopathology is yet to be fully realized, particularly for children and adolescents suffering from emotional disorders (Wren, Scholle, Heo, & Comer, 2003, 2005). Long-standing cultural beliefs and expectations regarding the nature of psychopathology and its relevance to traditional medicine have likely interfered with the implementation of truly integrated care. Primary care physicians and mental health specialists currently function and interact across parallel, yet overlapping care delivery systems – one primarily concerned with the management of physical disease in the biomedical tradition and the other focused on the management of psychopathology, the ostensible mental analog of physical disease.

Children and adolescents presenting with physical symptoms and complaints that are medically unexplained after routine medical assessment, commonly referred to as functional somatic symptoms (FSS), present special challenges to existing care delivery.
models and conceptualizations of illness and disease. Prior to the work of Pasteur and Koch, symptoms themselves were largely the focus of medical practice, with relatively little attention paid to causality (Carter, 1980; Fabrega, 1990). The biomedical model created a seismic shift in medical practice, differentiating the subjective and symptomatic suffering of patients, commonly referred to as illness, from the biophysical reality of disease, with the fundamental premise of the biomedical model being that illness is caused by disease (Weiner & Fawzy, 1989). Consequently, a core element of modern medical training involves learning how to determine if a given patient’s illness can be adequately explained by a concomitant disease, often by a process of exclusion or ‘ruling out’ (Chambers, 2003). This means that the first step in generating a differential diagnosis in a patient with presumably unexplained symptoms is to seriously consider the possibility of unrecognized physical disease.

While the legitimacy of illness judged to be due to physical disease is typically unquestioned and such illness is viewed as being outside the patient’s voluntary control, medically unexplained symptoms may be viewed as being of questionable legitimacy within the prevailing culture and thus representative of some moral failing on the part of the patient (Weiner & Fawzy, 1989). Patients and physicians appear to behave with an implicit understanding of the cultural expectations associated with the sick role as described by Talcott Parsons (1964), which include that the sick are considered blameless for their condition and may be exempted from usual duties and obligations only if the sick role is sanctioned by a physician, the cultural arbiter of whether a particular illness is deemed legitimate. One risk inherent in this approach is that a physician’s statement that ‘I can’t find anything wrong’ (i.e., ‘I find no evidence of disease in the biomedical sense’) can easily be misunderstood by the patient (and sometimes the physician) to mean that ‘nothing is wrong’ (i.e., ‘this is not a real problem’). Such statements by a physician are easily experienced by the patient and family as empathic failures, or even worse, as accusations that the patient is somehow guilty of requesting help for imagined, fabricated, or self-generated suffering.

The notion of psychopathology developed in an effort to understand and describe common clinical presentations where overt disease could not be found, with the word neurosis being coined to describe illnesses where nervous system disease was expected, but could not be proven. Neurosis encompassed a variety of overlapping physical and cognitive symptoms that are now categorized among the anxiety, depressive and somatoform disorders of current psychiatric nosology (American Psychiatric Association, 2000). Despite modern efforts to parse the components of ‘neurosis’ and validate anxiety, depressive, and somatoform disorders as being distinct from one another, evidence in limited and debate about the nature of the relationship between these commonly overlapping disorders is ongoing (e.g., Andrews, 1996). Just as the term pathology refers to both the branch of medicine concerned with the scientific study of disease, as well as the definable changes in bodily tissues and organs associated with disease (i.e., the biophysical distortions of the normal condition associated with specific diseases), the term psychopathology came to be jointly applied to the discipline devoted to studying the phenomena of mental disorders (Stanghellini, 2009) and to the distortions, disturbances, or degenerations of normal psychosocial functioning considered to be characteristic of particular mental disorders (Toth & Cicchetti, 2010). A psychological model of illness causation thus developed in parallel with the biomedical model, with explanations initially being sought in terms of causal psychological factors, conflicts, and/or traumas - the psychosocial analogs of infectious agents (Carter, 1980; Freud, 1896).

Although the biopsychosocial model (Engel, 1977) arose from the need to integrate these seemingly parallel viewpoints and models, everyday medical practice has continued to reify false dichotomies between physical and mental health and a dualistic approach to patient care. Despite academic acceptance that health is best viewed as a unitary construct that cannot justifiably be parsed into physical and mental health, existing systems of care delivery apply different standards of diagnosis, regulation, and reimbursement to health problems conceptualized as being physical as opposed to those conceptualized as being mental. This is particularly unfortunate in the primary care and general medical settings where patients with FSS, anxiety, and depression typically present.

Children and adolescents with FSS are both conceptually and practically puzzling to pediatricians, other health care providers, and mental health professionals. They are ‘neither fish nor fowl’, presenting with symptoms that are subjectively physical, yet objectively without explanatory pathology, and commonly associated with anxiety and depressive symptoms and disorders (e.g., Campo et al., 2004). Efforts to conceptualize FSS may take place on the individual somatic symptom level, as part of a syndromic cluster known as a functional somatic syndrome (e.g., chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome) – the practice most common in general medicine, or as representative of a psychiatric disorder such as an anxiety, depressive, or somatoform disorder. Regardless, the diagnostic constructs for patients with medically unexplained physical symptoms used in general medicine and psychiatry are an acknowledgment that genuine disorders associated with suffering and impairment may exist in the absence of explanatory physical disease. Once
unrecognized physical disease is eliminated as a plausible explanation for the physical symptoms, psychiatric differential diagnosis becomes focused on whether the patient appears to have voluntary control over the symptom, as in factitious disorder, factitious disorder by proxy, and malingering, or whether the symptom is experienced by the patient as being outside voluntary control, as in somatoform, anxiety, and mood disorders.

**Somatoform disorders** are characterized by the presence of distressing and/or impairing physical symptoms that are not fully explained by a general medical condition, another psychiatric disorder, or the use of a particular substance. In contrast to factitious disorder and malingering, somatoform disorders are not considered to be intentionally produced or under the voluntary control of the patient (American Psychiatric Association, 2000). The diagnostic category of somatoform disorders has been the subject of considerable debate. The argument to abolish or significantly modify the category has been rooted in concerns that the category is intrinsically dualistic and culturally bound, and that the diagnoses themselves are unreliable, ambiguous, and poorly accepted by patients, families, and practitioners of general medicine (Mayou, Kirmayer, Simon, Kroenke, & Sharpe, 2005).

Although anxiety and depressive symptoms and disorders are no less ‘medically unexplained’ than FSS, current psychiatric nosology suggests that the presence of one or several FSS may be ‘explained’ by the presence of an associated anxiety or depressive disorder (American Psychiatric Association, 2000). Because physical symptoms are also included in the diagnostic criteria for anxiety and depressive disorders, the clinician must determine whether observed FSS should be considered to be part and parcel of an associated anxiety and/or depressive disorder, introducing considerable subjectivity into the process of categorical diagnosis. This practice of ‘explaining’ the presence of one medically unexplained symptom by virtue of its association with a constellation of other biomedically unexplained symptoms appears to confound psychopathology with pathology. Such diagnostic conventions highlight our relatively poor understanding of the relationship between common FSS, anxiety, and depression. Given a growing appreciation that emotion and feelings are not equivalent and are managed by different areas of the brain (LeDoux, 1998), it appears reasonable to consider the possibility that FSS may be representative of emotional disorder, regardless of whether cognitive symptoms of anxiety or depression are recognized. This paper reviews existing knowledge regarding the association of common pediatric FSS with anxiety and depressive symptoms and disorders across the life span, with the aim of informing efforts to improve existing psychiatric conceptualizations and nosology, as well as practical clinical management.

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**Functional somatic symptoms: epidemiology and relevance**

**Overview**

Medically unexplained physical symptoms or FSS have historically been recognized as important and problematic aspects of pediatric practice (e.g., Apley & Naish, 1958; Richards, 1941; Wylie & Schlesinger, 1933). Reviews over the past two decades have documented that FSS are common in community-based and clinical samples of children and adolescents, are more prevalent in girls and with increasing age into adolescence, and are associated with individual suffering and impairment, including poor school attendance and performance, interpersonal and social difficulties, and self-perceived health limitations (e.g., Campo & Fritsch, 1994; Campo & Fritz, 2007; Campo & Garber, 1998; Eminson, 2007; Fritz, Frisch, & Hagino, 1997; Garralda, 1999; Schulte & Petermann, 2011). FSS are particularly common in pediatric primary care (Campo, Jansen-McWilliams, Comer, & Kelleher, 1999; Garralda & Bailey, 1987, 1990), and have been associated with higher levels of health service use and school problems (Campo, Comer, Jansen-McWilliams, Gardner, & Kelleher, 2002). Although FSS appear to be more prevalent in girls overall (Berntsson & Kohler, 2001; Campo & Fritsch, 1994; Eminson, 2007), age may be a factor, with some studies finding a relatively equal gender ratio in childhood followed by a preponderance of female symptom reporting in adolescence (Campo et al., 1999, 2002; Dhossche, Ferdinand, Van der Ende, & Verhulst, 2001; Santalahti, Aromaa, Sourander, Helenius, & Piha, 2005; Steinhausen & Metzke, 2007) and others reporting higher rates of female symptom reporting across both childhood and adolescence (Perquin et al., 2000; Rask et al., 2009). Although patients and families typically focus on a single symptom at the time of clinical presentation, the presence of one somatic complaint predicts another, with headache and abdominal pain appearing to be the most common combination (Alfven, 1993a; Larsson & Sund, 2007; Perquin et al., 2000; Rask et al., 2009; Santalahti et al., 2005).

**Limitations of existing research**

Unfortunately, interpreting the collective results of existing research on FSS in children and adolescence has been complicated by a number of methodological limitations and variations in study design and execution. Most studies have not included the use of an independent medical evaluation to determine the likelihood that reported symptoms are truly medically unexplained. Sources of assessment information vary from child or parent reports alone, to combined child and parent reports, and to reports by teachers or clinicians. Both clinical and community-based samples have been examined,
typically using different assessment instruments and approaches, and the threshold for counting any given somatic symptom report as significant varies across studies. For example, some studies demand that functional impairment or medical help-seeking is necessary for a symptom to be considered meaningful, whereas others do not. While some studies focus on individual symptoms (e.g., abdominal pain, fatigue), others focus on clusters of symptoms within a given organ system (e.g., gastrointestinal complaints, musculoskeletal pains) or symptom groupings representative of functional somatic syndromes (e.g., chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome), while still others apply a general checklist of commonly reported somatic complaints. The time frame and the age of subjects assessed have also varied across studies, with many relying upon retrospective recall, and assessments for emotional and behavioral problems and disorders have been included inconsistently. Studies that have included assessments for emotional symptoms and psychiatric disorders have varied in the respondents used (e.g., child, parents, and/or teachers) and in assessment methods (e.g., questionnaires, interviews), focus (e.g., symptoms, disorders), and content (e.g., anxiety, depression, internalizing symptoms, anxiety and depression, somatoform disorders, general psychopathology). In general, studies have typically focused on assessing and reporting functional somatic symptoms and syndromes rather than the presence of somatoform and other psychiatric disorders.

**Prevalence**

Several community-based studies highlight the prevalence of FSS in childhood and adolescence, and document that the presence of any one FSS tends to be associated with the presence of others. Nearly one-half of 540 3rd to 12th graders endorsed at least one somatic symptom in the prior 2 weeks, with headaches, fatigue, musculoskeletal and abdominal pains being the most commonly reported symptoms (Garber, Walker, & Zeman, 1991). FSS appear to be prevalent in preschoolers as well, with 20% of 3- to 5-year-old Spanish children experiencing at least one somatic symptom (Domenech-Llaberia et al., 2004). In a sample of over 10,000 Nordic children aged 2–17 years, at least one FSS was reported by 13% of 2- to 6-year olds, 17% of 7- to 12-year olds, and 23% of 13- to 17-year olds (Bennetsson & Kohler, 2001). Another more recent study assessed FSS in over one thousand 5- to 7-year-old Danish children and reported the 1-year prevalence of any FSS to be 23%, with limb pain, headaches, and stomachaches being the most common complaints; approximately 40% of children with FSS reported multiple other somatic symptoms, and multiple FSS were associated with greater impairment (Rask et al., 2009). Several other studies have found that FSS tend to cluster, with 12%–15% of three different pediatric samples reporting at least four different FSS (Belmaker, Espinoza, & Pogrud, 1985; Garber et al., 1991; Vila et al., 2009). Offord et al. (1987) identified a ‘multiple somatic complaints syndrome’ in 11% of adolescent girls and 4.5% of boys in a large community-based study in Canada.

The Early Developmental Stages of Psychopathology Study is the only available study that assessed somatoform disorders in a community-based sample of adolescents and young adults (Lieb et al., 2002). Somatoform syndromes and disorders were found in 12.5% of the sample, and were more common in females. The most prevalent disorder was pain disorder, and conversion disorder was quite rare. The presence of any somatoform disorder was reported to be relatively stable and enduring, particularly for females, with approximately half of subjects remitting over an average follow-up period of 3–4 years. However, even though approximately half of all cases were persistent, there was considerable fluctuation and transition noted between different types of somatoform disorders.

With regard to specific unexplained somatic symptoms, headache appears to be most prevalent in school aged children and adolescents, reported on a weekly basis by approximately 10 to 30% (Egger, Costello, Erkanli, & Angold, 1999; Fichtel & Larsson, 2002; Larsson, 1991; Oster, 1972) and the ostensibly reason for 1 to 2% of all pediatric office visits (Starfield et al., 1980). Abdominal pain sufficient to be associated with impairment is reported by 7%–5% of school aged children and adolescents (Apley & Naish, 1958; Chitkara, Rawat, & Talley, 2005), is the most common somatic complaint in preschool children (Domenech-Llaberia et al., 2004; Zuckerman, Stevenson, & Bailey, 1987), and accounts for 2%–4% of pediatric office visits (Starfield et al., 1980). Other commonly reported pains include chest pain, limb pain, and back pain (Campos & Fritsch, 1994; Garber et al., 1991). Musculoskeletal pains were reported at least weekly in a study of Finnish youth, with nearly 10% endorsing multiple pain sites and approximately 1% meeting criteria for the functional somatic syndrome known as fibromyalgia (Mikkelsen, Sourander, Phia, & Salminen, 1997).

Regarding complaints other than pain, fatigue is exceptionally common, with up to one-half of adolescents complaining of at least weekly fatigue and 15% reporting daily fatigue (Belmaker et al., 1985; Garralda & Chalder, 2005; Larsson, 1991). Chronic fatigue syndrome (CFS) is a functional somatic syndrome defined by at least 6 months of severe fatigue, musculoskeletal pains, sleep difficulties, and problems with concentration and short-term memory, with available studies suggesting a prevalence in adolescents of less than 1% (Garralda & Chalder, 2005). Other common pediatric FSS include complaints of dizziness and lightheadedness, as well
as gastrointestinal symptoms such as nausea, vomiting, and bowel-related complaints, which are often, but not always reported in association with abdominal pain (Campo & Fritsch, 1994; Garber et al., 1991). Conversion symptoms – essentially medically unexplained deficits of consciousness, sensation, or motor function such as nonepileptic seizures, gait or movement abnormalities, and ‘hysterical’ blindness or paralysis – tend to be seen primarily in specialty clinics and tertiary settings, and are relatively rare in community samples and in primary care (Lieb et al., 2002; Stefansson, Messina, & Meyerowitz, 1976; Tomasson, Kent, & Coryell, 1991).

**Association of functional somatic symptoms with anxiety and depression**

**Cross-sectional associations**

**Multiple somatic symptoms.** The preponderance of evidence suggests that children and adolescents with FSS in community samples are significantly more likely than unaffected peers to experience anxiety and depressive symptoms (Campo & Fritsch, 1994; Dhossche et al., 2001; Egger, Angold, & Costello, 1998; Egger et al., 1999; Eminson, Benjamine, Shortall, Woods, & Faragher, 1996; Garber et al., 1991; Haavisto et al., 2004; Harma, Kaltiala-Heino, Rimpela, & Rantanen, 2002; Larsson, 1991; Poikolainen, Kanerva, & Lonnqvist, 1995; Santalahti et al., 2005; Taylor, Szatmari, Boyle, & Offord, 1996). The majority of community-based studies of pediatric FSS have used self- or parent report questionnaires and most often have assessed multiple FSS rather than specific single somatic symptoms. Internalizing symptoms of anxiety and depression were assessed in some studies of FSS, but not others, and a variety of self and parent report questionnaires have been used, with the internalizing scale of the Child Behavior Checklist (CBCL) or Youth Self Report (YSR) being among the most commonly applied measures. Preschool children with multiple FSS experience more emotional and behavioral problems than peers, most notably anxiety (Domenech-Llaceria et al., 2004). Several large community-based studies have also shown a consistent association between reports of multiple FSS and depressive symptoms in older children and adolescents (Bohman et al., 2010; Haavisto et al., 2004; Santalahti et al., 2005).

The Great Smoky Mountains Study employed the standardized Child and Adolescent Psychiatric Assessment (CAPA) interview to generate psychiatric diagnoses, and found that stomachaches and headaches together were associated with anxiety disorders in girls, with nearly 70% of girls with both somatic symptoms meeting criteria for an anxiety disorder (Egger et al., 1999). Musculoskeletal pains were associated with anxiety and depression in girls and with depression in boys, and there was a statistically nonsignificant trend suggesting a possible association between abdominal pain and anxiety disorders in boys. The investigators also found associations between headaches and conduct disorder, as well as between abdominal pain and oppositional defiant disorder, in boys (Egger et al., 1998). In addition to associations between FSS and symptoms of traditional emotional disorders, other investigators have reported that disruptive behavioral problems may also be significantly associated with FSS in both girls and boys in community samples (e.g., Santalahti et al., 2005; Taylor et al., 1996).

In a study of over 20,000 primary care visits by children aged 4–15 years, children with frequent complaints of pain and a history of visits to the doctor for medically unexplained symptoms endorsed more emotional and behavioral problems than unaffected controls, with ‘somatizers’ reporting significantly more internalizing symptoms and nearly 50% screening positive for psychopathology on the Pediatric Symptom Checklist (Campos et al., 1999). Of subjects with frequent aches and pains, 34% scored above the screening threshold for internalizing disorders (Campos et al., 2002).

Higher numbers of FSS are associated with a greater likelihood of anxiety and depressive symptoms, suggesting an apparent ‘dose–response’ relationship between FSS and internalizing symptoms in many studies (Dhossche et al., 2001; Harma et al., 2002; Larsson & Sund, 2007; Little, Williams, Puzanova, Rudzinski, & Walker, 2007). Similarly, functional impairment in youth with FSS has been associated with the presence of internalizing symptoms, most robustly with the presence of depression (Claar & Walker, 2006; Egger et al., 1998; Gauntlett-Gilbert & Eccleston, 2007; Wendland, Jackson, & Stokes, 2010).

**Abdominal pain.** Apley and Naish (1958) reported that ‘emotional disturbances’ such as undue fearfulness and sleep and appetite difficulties were more prevalent in children with functional abdominal pain (FAP) than unaffected comparison subjects in a community sample, but standardized measures of psychopathology were not used. In a community study of 3-year-old children, those with FAP were significantly more likely to exhibit emotional and behavioral problems (26% vs. 10%), ‘dependence’ (26% vs. 10%), and fearfulness (18% vs. 11%) than pain-free children (Zuckerman et al., 1987). Faull and Nicol (1986) found that 6 year old children with FAP in a community sample of 494 second graders in the UK were more likely to score beyond the cut-off on the Rutter A(2) behavior scale than unaffected children and to be rated as ‘hyperactive’ by their parents. In a community-based study of adolescents, those with FAP who met criteria for irritable bowel syndrome (IBS; a functional somatic syndrome...
characterized by FAP and associated bowel complaints) scored significantly higher on trait anxiety and depressive symptoms than children without IBS, with 23% of older adolescents with IBS scoring at or beyond the cutoff for depression on the Child Depression Inventory compared to 8% of those without IBS (Hyams et al., 1996). Trait anxiety correlated positively with the severity, frequency, and duration of abdominal pain, as did depressive symptoms on the Children’s Depression Inventory (CDI) with the severity and frequency of abdominal pain (Hyams et al., 1996). Saps et al. (2009) assessed 237 third through eighth grade students weekly for multiple somatic symptoms and found that persistent abdominal pain was associated with significantly higher levels of anxiety and depressive symptoms. Over 20,000 adolescents were assessed in the National Longitudinal Study in Adolescent Health, and the 3% who reported daily abdominal pain were significantly more likely to experience depression and impairment than peers, with 45% of daily pain sufferers scoring above the instrument cutoff on the Center for Epidemiologic Studies Depression Scale (CES-D) as compared to 16% of the general population of adolescents (Yousef, Atienza, Langseder, & Strauss, 2008). In a community sample of Dutch schoolchildren aged 7–18 years, FAP was significantly associated with anxiety and depression symptoms and other FSS on univariate analysis, and remained significantly associated with depressive and other somatic symptoms on multivariate analysis (Van der Veek, Derkx, de Hann, Benninga, & Boer, 2010).

With rare exception (McGrath, Goodman, Firestone, Shipman, & Peters, 1983), clinically referred children with FAP also exhibit significantly higher levels of internalizing symptoms than well children (Campo et al., 2004; Dorn et al., 2003; Galli et al., 2007; Garber et al., 1990; Walker, Garber, & Greene, 1993; Walker & Greene, 1989). FAP and symptoms of anxiety are consistently and robustly associated across studies (Campo et al., 2004; Garber et al., 1990; Hodges, Kline, Barbero, & Woodruff, 1985a; Walker et al., 1993), and most studies also report significant associations between FAP and depression (Campo et al., 2004; Garber et al., 1990; Hyams et al., 1996; Liakopoulou-Kairis et al., 2002; Walker & Greene, 1989; Walker et al., 1993), though a few find no significant between group differences (Hodges, Kline, Barbero, & Flaney, 1985b; McGrath et al., 1983). Walker et al. (1993) compared 88 children and adolescents with FAP to a group with gastrointestinal disease, a psychiatric comparison group with mood and anxiety disorders, and a well comparison group who had been treated for acute minor illness or injury. FAP children experienced significantly more internalizing symptoms of anxiety and depression than well children, did not differ significantly from the gastrointestinal group, and exhibited similar levels of trait anxiety, but fewer internalizing and externalizing behavioral problems than the psychiatric group (Walker et al., 1993).

Most studies of clinically referred children and adolescents with FAP that have investigated psychopathology as a domain have relied on data gleaned from questionnaires, but a few studies in the literature have employed standardized psychiatric assessments conducted by interviewers blind to physical health history (Campo et al., 2004; Garber et al., 1990; Ghanizadeh et al., 2008; Hodges et al., 1985a; Liakopoulou-Kairis et al., 2002). In a study that compared 30 children with FAP to 42 well and 67 psychiatric controls using an early version of the Child Assessment Schedule (CAS) that did not generate psychiatric diagnoses, Hodges et al. (1985a) found higher anxiety symptom scores in the FAP group than in well controls. The psychiatric group scored significantly higher than the FAP group on all symptom complexes other than anxiety, and the FAP and well groups differed from one another only on measures of anxiety.

Garber et al. (1990) compared 13 children with FAP to 19 psychiatric, 11 gastrointestinal disease, and 16 well controls. All children in the FAP group met criteria for a psychiatric diagnosis based on the K-SADS, with 11 of 13 (85%) meeting criteria for an anxiety disorder and 5 of 13 (38%) meeting criteria for major depressive disorder (MDD). High rates of anxiety and depression symptoms and disorders significantly distinguished FAP subjects from well controls, but not from the gastrointestinal and psychiatric controls; the psychiatric group exhibited more disruptive behavior problems than the FAP and other groups.

Liakopoulou-Kairis et al. (2002) reported that 82% of children and adolescents with FAP met criteria for a psychiatric disorder, with 42% suffering from at least one anxiety disorder and 26% meeting criteria for a depressive disorder. FAP subjects were significantly more likely to suffer from psychiatric and emotional disorders than well controls, but exhibited rates of psychiatric, anxiety, and depressive disorders very similar to those of a comparison group of children and adolescents with headache. An Iranian study that applied a Farsi version of the K-SADS found significantly higher rates of psychiatric disorders in children and adolescents with FAP than in pain free controls or in controls with gastrointestinal disease (Ghanizadeh et al., 2008). Approximately half of FAP subjects suffered from a psychiatric disorder, with the most common diagnoses including separation anxiety and major depressive disorders.

A case–control study of FAP in primary care compared 42 children and adolescents with FAP to 38 pain-free controls using the K-SADS-PL and found significantly higher rates of anxiety disorders in FAP subjects (79% vs. 10% controls), with separation anxiety disorder, generalized anxiety disorder, and social phobia being the most common diagnoses.

Depressive disorders were also more common in the FAP group (43% vs. 8% of controls), with 31% of FAP subjects experiencing a major depressive disorder. Another small study compared 14 children with FAP to well controls and children with anxiety disorders (Dorn et al., 2003). The FAP group reported the highest levels of somatic symptoms, the anxiety group scored highest on specific measures of depression and anxiety, and the FAP and anxiety groups scored similarly on the internalizing and externalizing scales of the CBCL. The groups were also compared using physiologic measures that included heart rate, systolic blood pressure (SBP), and salivary cortisol in response to the Trier Social Stress Test for Children (TSSTC). Although statistically significant between groups differences were not identified on most measures, the anxiety and FAP groups both exhibited higher baseline SBP than well controls, with a statistically significant difference for the anxiety group and a nonsignificant trend for the FAP group (Dorn et al., 2003).

In a study that compared 21 FAP subjects aged 8–16 years to well controls and an anxiety disordered group, 67% of FAP subjects met criteria for an anxiety disorder on the K-SADS-PL compared with 100% of the anxiety disordered group and 6% of well children (Dufton, Dunn, & Compas, 2009). FAP subjects exhibited significantly higher levels of internalizing and specific anxiety symptoms than well controls, but symptom levels were similar overall for the FAP and anxiety disorder groups.

**Headache.** Studies of children and adolescents with recurrent headache recruited from clinical and community samples have most often supported an association between recurrent headaches and anxiety and/or depressive symptoms and disorders (Anttila et al., 2004; Battistutta, Aliverti, Montico, Zin, & Carrozz, 2009; Boz et al., 2004; Egger et al., 1998; Fearon & Hotopf, 2001; Fichtel & Larsson, 2002; Galli et al., 2007; Harma et al., 2002; Kroner-Herwig, Morris, & Heinrich, 2008; Larsson, 1991; Liakopoulou-Kairis et al., 2002; Mazzone, Vitiello, Incorpora, & Mazzone, 2005; Pakalnis, Butz, Splaingard, Kring, & Fong, 2007; Smith, Martin-Herz, Womack, & Marsigan, 2003), though some studies have yielded mixed (Holroyd, France, Nash, & Hursey, 1993; Vannatta et al., 2008) or negative results (Cooper, Bawden, Camfield, & Camfield, 1997). Headaches reported by children and adolescents were significantly associated with anxiety and depressive symptoms in several large European epidemiologic samples (Anttila et al., 2004; Fichtel & Larsson, 2002; Larsson, 1991; Kroner-Herwig, Morris, & Heinrich, 2008). Investigators in the Great Smoky Mountains study found that 9- to 15-year-old children with a psychiatric disorder were twice as likely to suffer from headaches as those without a psychiatric disorder, and that depressed and anxious girls had a fourfold and threefold greater likelihood of suffering from headaches than unaffected controls, respectively; although the prevalence of headaches was similar for boys and girls in the overall sample, the association of headache with internalizing disorders was not found for boys, who were more likely to suffer from headaches in the presence of a conduct disorder (Egger et al., 1998). Liakopoulou-Kairis et al. (2002) reported that 84% of children and adolescents with headache met criteria for a psychiatric disorder on the K-SADS, with the most prevalent diagnoses being anxiety disorders (35%) and depressive disorders (23%). Efforts to explore differences in internalizing symptoms between different types of headaches such as migraine and tension type headache have typically failed to show marked differences with regard to anxiety and depressive symptoms between the groups (Boz et al., 2004; Galli et al., 2007; Gladstein & Holden, 1996).

**Chest pain.** Children and adolescents with functional chest pain reported significantly higher levels of anxiety symptoms and anxiety sensitivity than a comparison group of other 7- to 18-year olds with benign heart murmurs; there was a trend suggesting higher levels of depressive symptoms and harm avoidance in the chest pain group (Lipsitz et al., 2004). Uncontrolled studies that used a standardized psychiatric interview to assess children and adolescents with unexplained chest pain found that 81% of those presenting to a specialty cardiac clinic and 56% of those presenting to the emergency department met criteria for diagnosis of an anxiety disorder (Lipsitz et al., 2005, 2010). In a subsequent controlled study, psychiatric disorder was significantly more likely in youth presenting with chest pain in a specialty cardiac setting than in controls, with 74% of the chest pain group meeting criteria for a psychiatric disorder, with the most prevalent diagnosis being that of an anxiety disorder (Lipsitz et al., 2012).

**Musculoskeletal pain.** In a community-based study of third to fifth grade students in Finland, children with complaints of musculoskeletal pain were significantly more likely to have higher levels of parent reported internalizing symptoms and child reported depressive symptoms than healthy controls (Mikkelsen et al., 1997). Children with multiple symptoms of musculoskeletal pain reported significantly higher levels of depressive symptoms than those with a single complaint of pain. Participating children with juvenile fibromyalgia, a clinically described syndrome characterized by widespread musculoskeletal pain, multiple tender points in the muscles, and associated symptoms such as sleep problems, fatigue, headaches, and abdominal complaints, had higher levels of depressive symptoms than subjects with musculoskeletal pain alone.
Anxiety disorders. High than expected rates of FSS have been reported in children and adolescents suffering from anxiety disorders (Beidel, Christ, & Long, 1991; D’Hoosche et al., 2001; Ginsburg, Rid-
symptoms and disorders across the life span is particularly challenging due to considerable variability in the methodological approaches taken in individual studies. For one thing, outcome and predictor variables vary across studies. Some studies begin by examining the longitudinal outcomes for subjects with a single FSS at time 1, while others focus on following subjects experiencing a cluster of multiple FSS or internalizing psychiatric symptoms, and still others track subjects with a specific functional somatic syndrome (e.g., chronic fatigue syndrome) or psychiatric disorder. Similarly, time 2 outcome variables, assessment measures, and length of follow-up period vary considerably across studies. Many studies do not include assessments for the desired outcome within the baseline assessment battery, making it difficult to determine if a particular outcome at the follow-up assessment was truly ‘predicted’ by a particular symptom or disorder or whether the association observed at time two simply reflected a stable, but undocumented baseline association.

Somatic symptoms and disorders as predictors. Several important community-based epidemiologic studies have contributed greatly to our understanding of the relationship between FSS and psychiatric symptoms and disorders across the life span, with relative consistency in noting that childhood and adolescent FSS are positively associated with psychiatric symptoms and disorders later in life, particularly anxiety and depression (Dhossche et al., 2001; Haavisto et al., 2004; Hotopf, Carr, Mayou, Wadsworth, & Wessely, 1998; Janssens, Rosmalen, Ormel, van Oort, & Oldehinkel, 2010; Sourander et al., 2005a,b; White & Farrell, 2006; Zwaigenbaum, Szatmari, Boyle, & Offord, 1999). Janssens et al. (2010) found that anxiety and depressive symptoms also had a strong contemporaneous effect on FSS in addition to a predictive effect, whereas the effect of FSS on the presence of anxiety and depression was weaker and associated with a time lag. Single FSS typically predict multiple FSS later in life (Dhossche et al., 2001; Hotopf, Mayou, Wadsworth, & Wessely, 1999; Lieb et al., 2002; Steinhausen & Metzke, 2007), though occasionally specific symptoms have homotypic predictive power as well (Steinhausen & Metzke, 2007).

The Medical Council Survey of Health and Development established a national birth cohort of subjects born in the UK in 1946 and conducted several waves of data collection across the life span, with standardized psychiatric interview assessments being conducted at ages 36 years (Hotopf, 2002). Persistent childhood abdominal pain was associated with adult psychiatric disorders, particularly anxiety and depressive disorders (Hotopf et al., 1998), multiple FSS (Hotopf et al., 1999), and hospitalizations for FSS (Hotopf, Wilson-Jones, Mayou, Wadsworth, & Wessely, 2000). Interestingly, proven physical disease in childhood was not associated with adult FSS or related hospitalizations (Hotopf et al., 1999; Hotopf et al., 2000). FAP identified in 6 year old children was significantly associated with the presence of anxiety disorder one year later in the Avon Longitudinal Study of Parents and Children (Ramchandani, Fazel, Stein, Wiles, & Hotopf, 2007). Frequent headaches in childhood predicted headache, other FSS, and psychiatric disorder in adulthood in another epidemiologic child development study in the U.K., (Fearon & Hotopf, 2001). Children whose teachers described them on the Rutter B questionnaire as having ‘frequent aches and pains’, appearing to be ‘miserable/unhappy’, and/or as often being off school for trivial reasons in the Aberdeen Child Development Study were significantly more likely than peers to rate themselves as being ‘permanently sick and disabled’ in adulthood; being perceived as ‘fearful/afraid’ by teachers was weakly associated with self-rated adult disability on univariate, but not multivariate analysis (Henderson, Hotopf, & Leon, 2009).

In the Ontario Child Health Study, the presence of multiple FSS in early adolescents without apparent emotional disorder significantly predicted major depressive disorder and panic attacks 4 years later, with the risk of subsequently developing a psychiatric disorder for young adolescents with multiple FSS and no evident psychiatric disorder being essentially equal to the risk for those with documented emotional distress (Zwaigenbaum et al., 1999). A large Finnish study determined that higher levels of self-reported FSS in childhood were significantly associated with an increased risk of anxiety and depressive symptoms, deliberate self-harm, and psychiatric disorder in later adolescence and at the time of military call-up examinations (Haavisto et al., 2004; Sourander et al., 2005a,b, 2006). Complaints of headache and abdominal pain in a community-based sample of urban children in the U.S. predicted higher levels of anxiety symptoms 6 months later (White & Farrell, 2006).

A large longitudinal population-based study of Dutch adolescents reported that FSS did not appear to predict future anxiety and depressive disorders when current psychiatric symptoms were included in the regression model, but strong cross-sectional associations between FSS and anxiety and depression were demonstrated at each study assessment point (Dhossche et al., 2001). Young adults with a history of FSS in adolescence were significantly more likely to be diagnosed with anxiety and depressive disorders in young adulthood than controls, but were not more likely to be diagnosed with antisocial problems or substance abuse. Study results suggest that the association between FSS, anxiety, and depression is stable over time, as well as relatively specific to the emotional disorders. The issue of whether FSS are truly predictive of subsequent emotional symptoms and disorders may turn in large
measure on methodology across studies, since not all studies include measures of the longitudinal outcome variable in the baseline assessment.

Studies of clinical samples have also demonstrated that FSS in childhood and adolescence are associated with psychiatric symptoms and disorders upon subsequent follow-up assessment. In a small study of 28 young adults with a childhood history of FAP, FAP subjects were significantly more likely to experience anxiety symptoms and disorders as adults than a comparison group of 28 individually matched controls who had participated in a study of tonsillectomy and adenoidectomy in childhood (Campo et al., 2001). Former pediatric FAP patients were significantly more likely than controls to meet diagnostic criteria for current (20% vs. 0%) and lifetime anxiety disorders (46% vs. 18%) in young adulthood, and were approximately twice as likely to suffer from a lifetime depressive disorder (57% vs. 29%), though the latter difference did not reach statistically significance, likely given the small sample size. Childhood FAP patients also exhibited significantly higher levels of hypochondriacal fears and perceived themselves to be more physically impaired and vulnerable to the effects of physical symptoms in adulthood than controls (Campo et al., 2001). One retrospective study found that recollection of hypochondriacal worries in childhood was positively associated with hypochondriasis in adulthood (Noyes et al., 2002). A follow-up study of a clinical sample of 31 adolescents and young adults who had been diagnosed with FAP five years previously also reported higher levels of anxiety and depressive symptoms at follow-up for FAP subjects than unaffected controls (Walker, Garber, Van Slyke, & Greene, 1995). A longitudinal study of clinically recruited youth with juvenile fibromyalgia demonstrated higher levels of internalizing symptoms in affected subjects compared to healthy controls at the time of follow-up (Kashikar-Zuck et al., 2010b).

Anxiety and depressive symptoms and disorders as predictors. A number of studies have explored whether anxiety and depressive symptoms and disorders in childhood and adolescence predict FSS and functional somatic syndromes in adulthood. Baseline emotional problems were the only significant predictor of persistent complaints of pain in a large, population-based prevalence study, with childhood emotional problems serving to correctly classify pain status in 86% of subjects at time of two year follow-up (Perquin et al., 2003). Other studies have found that pediatric anxiety and/or depressive symptoms and disorders significantly predict future and persistent headaches (Guidetti et al., 1998; Larsson & Sund, 2005, 2007; Wang, Fuh, Lu, & Juang, 2007). In studies using standardized psychiatric interview assessments, headaches in adulthood were predicted by adolescent major depressive disorder (Pine et al., 1996) and by childhood anxiety and depressive disorders (Lee et al., 2009). Depressive symptoms at age 12 years were significantly associated with FAP in later adolescence in a population-based prospective study (Helgeland, Sandvik, Mathiesen, & Kristensen, 2010), and symptoms of emotional distress have been associated with persistence of abdominal pain in clinical samples (Mulvaney, Lambert, Garber, & Walker, 2006). Elevated scores on the Strengths and Difficulties Questionnaire in childhood were predictive of musculoskeletal pain in adulthood, but a specific association with childhood emotional distress was not demonstrated (Jones, Watson, Silman, Symmons & Macfarlane, 2003). In another study, chronic widespread pain in adulthood was predicted by parent and teacher reported symptoms on the Rutter A and B scales, but internalizing symptoms were not examined separately, making conclusions with regard to any association with emotional distress in childhood difficult (Pang, Jones, Power, & Macfarlane, 2010). With rare exception (Viner & Hotopf, 2004), anxiety and depressive symptoms in childhood and adolescence do appear to predict chronic fatigue later in life (Harvey, Wadsworth, Wessely, & Hotopf, 2008; Rimes et al., 2007; Viner et al., 2008; ter Wolbeek, van Doornen, Kavelaars, & Heijnen, 2008).

The Early Developmental Stages of Psychopathology Study (Lieb et al., 2002) longitudinally followed 3021 subjects aged 14–24 years at initial visit for an average of 3–4 years. The study is relatively unique in its application of the Munich Composite International Diagnostic Interview (M-CIDI), a standardized interview capable of diagnosing somatoform disorders, as well as preexisting anxiety, depressive, and substance use disorders. Baseline presence of an anxiety or depressive disorder was significantly associated with an increased risk of somatoform disorder onset, and persistence of somatoform disorder was associated with prior depression (Lieb et al., 2002).

Discussion
Review of existing cross-sectional and longitudinal studies of both community and clinical samples suggests that the presence of one or more FSS in childhood and adolescence is positively associated with presence of concurrent anxiety and depressive symptoms and disorders, and that pediatric FSS are significantly associated with multiple FSS, functional somatic syndromes, and an excess of anxiety and depressive symptoms and disorders later in life. Conversely, pediatric anxiety and depressive symptoms and disorders are significantly associated with FSS in childhood and adolescence, and increase the likelihood of FSS and functional somatic syndromes in adulthood. Methodological differences and limitations of existing studies make it difficult to determine to what degree functional somatic, anxiety, and depressive symptoms and disorders are truly predictive of one another or if the observed nonrandom
associations among the disorders are simply stable over time. A number of studies report proportionality between the number and intensity of pediatric FSS and levels of associated anxiety and depressive symptoms and disorders, with increasing numbers of FSS being associated with higher levels of anxiety and depression. The presence of internalizing symptoms, most notably depression, makes a significant contribution to the disability experienced by youth with FSS.

FSS, functional somatic syndromes, and somatoform disorders have also been reported to be strongly associated with anxiety and depressive symptoms and disorders in adults (Lieb, Meinlschmidt, & Araya, 2007), including in primary care settings (Lowe et al., 2008; Means-Christensen, Roy-Byrne, Sherbourne, Craske, & Stein, 2008; Mergl et al., 2007), and the presence of anxiety and/or depression contributes to the functional impairment reported by adults with FSS (Lowe et al., 2008).

There is a relative lack of continuity with regard to individual functional somatic symptoms and disorders over time, not unlike that observed with anxiety and depressive disorders, which tend to be more likely to cross-predict one another than the same specific disorder (i.e., homotypic prediction; e.g., Copeland, Shanahan, Costello, & Angold, 2009). Homotypic prediction thus appears to be less compelling for disorders characterized by FSS, anxiety, and/or depression than the ability of these related symptoms and disorders to predict one another (i.e., heterotypic prediction). Although previous efforts to better understand the problem of ‘comorbidity’ between the anxiety and depressive disorders have focused on paired associations, the relatively constant conjunction of FSS, anxiety, and depression across the life span suggests that including FSS in efforts to probe the relationship between anxiety and depression may help clarify the nature of clinical reality and assist in improving existing nosology.

Considered across the life span, there appears to be little objective evidence to support the notion that natural boundaries exist between anxiety, depressive, and functional somatic disorders, calling modern efforts to approach, classify, and treat them as separate entities into serious question. Artifact alone seems unlikely to account for the degree of comorbidity observed in existing studies, though it must be acknowledged that FSS are included in diagnostic criteria for the anxiety and depressive disorders, which overlap with existing diagnostic criteria for the somatoform disorders and functional somatic syndromes, potentially increasing the likelihood of diagnostic co-occurrence. Beyond artifact, options for understanding the nature of comorbidity include unidirectional causal models, where one disorder essentially causes the other or serves as a risk factor for the other, and shared vulnerability models, where presumably comorbid disorders share common risk factors or represent different aspects of a singular process (Merikangas & Stevens, 1997). Existing research has been insufficient to adequately answer questions regarding unidirectional causality, as the studies necessary to convincingly demonstrate temporal relationships among the various symptoms and disorders have not been accomplished. Nevertheless, the strength of observations that FSS, anxiety, and depression are significantly associated in childhood, adolescence, and adulthood offer some support for the notion that they may be manifestations of a common disorder or at least share common risk factors (Andrews, 1996). Observed associations between anxiety and depressive disorders (e.g., Kessler, 2000; Wittchen, Beesdo, Bittner, & Goodwin, 2003) have been attributed to a common diathesis, as well as to genetic pleiotropy, where diverse phenotypic consequences may result from a common genetic predisposition (Kendler, Gardner, Gatz, & Pedersen, 2007). For example, a specific functional polymorphism in the promoter region of the serotonin transporter gene has not only been associated with anxiety and exaggerated responses of the amygdala to novelty (Hariri et al., 2002), but also with depression in association with life adversity (Caspi et al., 2003), and with FSS (Yeo et al., 2004).

Circumstantially at least, known vulnerability factors such as female gender, increased somatotypic risk with increasing age into adolescence, history of exposure to life adversity, family history, and anxious or inhibited temperament are shared by individuals suffering from FSS, anxiety, and/or depression. There is also evidence that anxiety, depressive, and somatoform disorders/functional somatic syndromes respond to similar treatments, particularly to cognitive-behavioral psychotherapies and antidepressant medications, and that effective treatment of any one disorder appears to improve overall functional status and the symptoms of the comorbid disorders (Kroenke, 2007; Mayou, 2007). As with the emotional disorders, FSS are associated with a history of life adversity, with early life adversity and exposure to threat predicting functional somatic symptoms and disorders later in life (e.g., Craig, Boardman, Mills, Daly-Jones, & Drake, 1993; Fearon & Hotopf, 2001; Heim et al., 2009; Lieb et al., 2002; Paras et al., 2009). Anxiety and depressive symptoms and disorders in parents and family members have also been associated with heightened risk of FSS in childhood and adolescence (e.g., Campo et al., 2001, 2007; Garber et al., 1990; Hodges et al., 1985a; Zuckerman et al., 1987).

A preponderance of related temperamental characteristics such as behavioral inhibition, harm avoidance, neuroticism, trait anxiety, and negative affect has been reported in children and adolescents with FSS (Balague et al., 1995; Boz et al., 2004; Bursch, Walco, & Zeltzer, 1998; Campo et al., 2004; Davison, Faull, & Nicol, 1986; Manassis, Bradley, Goldberg, Hood, & Swinson, 1995; Muris & Mee-
stors, 2004). Such traits appear to correlate with pessimistic worry, fear of uncertainty, and a tendency to respond to environmental challenge at lower thresholds (Boyce, Barr, & Zeltzer, 1992; Kagan, Reznick, & Snidman, 1988). Emotional unawareness and negative affect have also been associated with child reports of FSS (Gilleland, Suveg, Jacob, & Thomasson, 2009). Anxiety sensitivity, the tendency to fear bodily sensations associated with anxious arousal based on a belief that the sensations signal serious bodily, psychological, or social harm, is significantly associated with FSS, most notably pain, in children and adolescents (Kroner-Herwig, Morris, & Heinrich, 2008; Lipsitz et al., 2004; Martin, McGrath, Brown, & Katz, 2007; Muris & Meesters, 2004; Tsao et al., 2009) and in adults (Asmundson & Katz, 2009). For example, patients with chronic fatigue and their families are often reported to fear that exertion and normalization of activities will lead to serious and lasting harm, a mindset that can interfere with successful management (Garralda & Chalder, 2005).

Individuals with FSS may exhibit heightened individual sensitivities to respond to internal and external threats at lower thresholds than unaffected peers, as well as exhibit somatic hypervigilance and selective attention to threat (Asmundson & Katz, 2009). Children with FAP show a heightened sensitivity to detect visceral sensations, and exhibit a lower threshold for discomfort than unaffected children (Di Lorenzo et al., 2001; Iovino et al., 2009; Van Ginkel, Voskuilj, Benninga, Taminiau, & Boeckxstaens, 2001). Iovino et al. (2009) also report that emotional instability is associated with heightened visceral perception in youth with FAP. Other studies have reported a general hypersensitivity to sensory stimuli in children with FAP, including hypersensitivity to gastrointestinal sensations evoked by a water load (Walker et al., 2006) and excessive muscle tenderness and a lowered pressure-pain threshold (Alfvén, 1993b; Duarte, Goulart, & Penna, 2000). Like anxious children, children with FAP show an increased auditory startle reflex relative to controls, suggesting heightened emotional responsiveness and neuronal excitability in the FAP group (Bakker, Boer, Benninga, Koelman, & Tijssen, 2010). Attentional biases toward painful and other somatic stimuli have also been demonstrated in children with FAP, supporting the notion that children with FSS may be hypervigilant to bodily sensations (Beck et al., 2011; Hermann, Zohsel, Hohmeister, & Flor, 2008).

A tendency to respond to perceived threat in a manner that generates some combination of somatic and cognitive emotional distress appears to be a common feature shared by individuals with FSS, anxiety, and depression (Goldberg, Krueger, Andrews, & Hobbs, 2009). Modern conceptualizations consider emotions to be brain states associated with the perception of rewards or punishments that generate bodily responses critical to survival, and that develop in response to natural and learned triggers (LeDoux, 1998). Feelings are a secondary construct, representing awareness of emotion and being mediated by different brain regions. Both fear and pain can serve defensive neurobehavioral functions, steering individuals away from perceived threats and motivating adaptive behaviors. Pain signals a perceived threat to physical integrity, is accompanied by a wish to avoid additional distress, and typically engenders adaptive behaviors such as withdrawal or avoidance. Analogous to anxiety disorders where fear is inappropriate to context, functional pain can be thought of as pain that is inappropriate to context (i.e., signaling tissue damage or injury in spite of its absence). Might FSS, anxiety, and depression reflect a common emotional disorder, essentially a sense of ‘unwellness’ related to activation and disruption of emotional processes? An argument can be made that it might prove to be conceptually and practically superior to consider FSS, anxiety, and depression as being representative of a nonspecific emotional disorder, examine symptom combinations dimensionally, and only then consider whether there is justification for parsing out specific disorders of anxiety, depression, and somatic distress in the future. One potentially promising approach is the Research Domain Criteria (RDoC) initiative of the National Institute of Mental Health, which is exploring new ways to classify psychopathology based on dimensions of observable behavior and neurobiological measures (Insel et al., 2010).

The observed associations between FSS, anxiety, and depression also have significant clinical implications. Pediatric anxiety and depressive disorders are often unrecognized in primary care settings, with only approximately one in five affected youth being detected in primary care (Richardson, Russo, Lozano, McCauley, & Katon, 2010). Clinicians should have a high index of suspicion for undiagnosed psychiatric disorder, especially anxiety and depressive disorders, in children and adolescents presenting with FSS, and then make every effort to conduct appropriate assessments and ensure access to proper care. Clinicians should make a conscious effort to avoid being distracted from comorbid anxiety and depressive disorders by an inordinate focus on the presenting physical symptoms and a search for unrecognized physical disease. Conversely, youth suffering from known emotional disorders should be carefully assessed for associated FSS and functional somatic syndromes and managed accordingly.

Conclusion

Areas deserving further exploration in examining the nature of comorbidity between FSS, anxiety, and depression across the life span include careful studies of the temporal onset of respective disorders, familial and genetic commonalities, psychobiological
relationships, early and concurrent life adversity, and shared responses to treatments. Large, methodologically strong population-based longitudinal studies that collect comprehensive information on functional somatic, anxiety, and depressive symptoms and disorders, as well as known correlates such as life adversity, are needed to disentangle the nature of comorbidity by establishing temporal relationships between the various symptoms and conditions (Rosmalen, 2010). The inclusion of information on familial relationships and genetics, as well as the addition of psychobiological assessments that probe individual responses to threat and attentional biases, may prove critical to better understanding potential mechanisms underlying observed comorbidities and their meaning. Finally, despite the need for additional knowledge, what is currently known supports serious reconsideration of existing nosology and should encourage efforts to reconceptualize the relationship between functional somatic symptoms, anxiety, and depression.

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Key Points
- Functional somatic symptoms (FSS) in childhood and adolescence are consistently associated with anxiety and depressive symptoms and disorders, both cross-sectionally and longitudinally.
- The likelihood of concurrent anxiety or depression increases with the number of FSS.
- Pediatric anxiety and depressive symptoms and disorders are associated with a heightened likelihood of multiple FSS later in life.
- Strong, reciprocal associations between FSS, anxiety, and depression across the life span call existing nosology, which classifies these conditions as distinct disorders, into question.
- Clinicians should have a high index of suspicion for unrecognized anxiety and depression in patients presenting with FSS in general medical settings.

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