Functional dyspepsia: Are psychosocial factors of relevance?

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The pathogenesis of Functional Dyspepsia (FD) remains unclear, appears diverse and is thus inadequately understood. Akin to other functional gastrointestinal disorders, research has demonstrated an association between this common diagnosis and psychosocial factors and psychiatric morbidity. Conceptualising the relevance of these factors within the syndrome of FD requires application of the biopsychosocial model of disease. Using this paradigm, dysregulation of the reciprocal communication between the brain and the gut is central to symptom generation, interpretation and exacerbation. Appreciation and understanding of the neurobiological correlates of various psychological states is also relevant. The view that psychosocial factors exert their influence in FD predominantly through motivation of health care seeking also persists. This appears too one-dimensional an assertion in light of the evidence available supporting a more intrinsic aetiological link. Evolving understanding of pathogenic mechanisms and the heterogeneous nature of the syndrome will facilitate effective management. Co-morbid psychiatric illness warrants treatment with conventional therapies. Acknowledging the relevance of psychosocial variables in FD, the degree of which is subject to variation, has implications for assessment and management. Available evidence suggests psychological therapies may benefit FD patients particularly those with chronic symptoms. The rationale for use of psychotropic medications in FD is apparent but the evidence base to support the use of antidepressant pharmacotherapy is to date limited.

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alising a role for psychosocial factors in FD is within the biopsychosocial model of disease as suggested by Drossman[10]. In this model, functional gastrointestinal disorders are seen as having multifactorial, bi-directional, rather than unicausal, unidirectional aetiology. This integrative view of illness, adopts the understanding that biological, psychological and social factors interact and said interaction accounts for the symptoms experienced, the patient's behavioural response and the outcome of the disorder. Many investigators now consider the 'Brain-Gut Axis' (BGA) to be the anatomical substrate, mediating this interaction[11]. At the very least, it provides a rough neurobiological framework for reciprocal connections between the brain and the gastrointestinal tract[12]. As a concept, it has emerged consequent to a convergence of research into brain-gut interactions and the effect of stress on such exchanges. The BGA is central to the biopsychosocial model in FD. To elaborate briefly, this axis is bi-directional and integrative with input from sensory sources (sight, smell, etc.) and somatosensory/viscerosensory sources, modified by cognitions and affects, and a neural circuit in the central nervous system (CNS), the spinal cord, the autonomic nervous system (ANS) and enteric nervous system (ENS)[13]. Using this paradigm, chronic functional gastrointestinal symptoms can be seen as a result of dysregulation of intestinal motor, sensory and CNS activity, resulting from disturbance at some level of the BGA.

EVIDENCE TO SUPPORT AN ASSOCIATION BETWEEN PSYCHOSOCIAL FACTORS AND FUNCTIONAL DYSPESIA

A myriad of psychosocial factors have been examined in the literature in relation to FD. These include psychological distress, personality traits, social support, life-events and life-stresses including abuse and bereavement. The issue of Psychiatric Disorder co-morbidity is often addressed within the same context. The associations between a number of these variables and FD are outlined below.

Psychological morbidity

Studies have demonstrated a high prevalence of Psychiatric Disorder in patients with dyspepsia of unknown origin. In the midst of the debate concerning the significance of this relationship, speculation as to the potential for a shared pathophysiology has arisen[2]. The most common psychiatric co-morbidities in patients with functional dyspepsia are Anxiety Disorders, Depressive Disorders and Somatoform Disorders[6,13]. In a clinic based study, findings showed that 87% of patients with FD, compared to 25% of patients with organic dyspepsia, had a psychiatric diagnosis[6,13]. A larger study, utilising semi-structured psychiatric interview and psychometric tools, revealed that 34% percent of the FD patients versus 1% of the duodenal ulcer patients had a psychiatric diagnosis. Anxiety Disorders were again most common. A mere 1% of the healthy controls met criteria for a psychiatric diagnosis[6]. These findings are not consistent across studies but conflicting results may be explained by use of different sample populations. Interestingly, in contrast to the latter findings, an earlier study demonstrated no statistically significant difference between essential dyspepsia and duodenal ulcer patients on various psychometric test scores. However, elevated levels of neuroticism, anxiety and depression were demonstrated in FD patients compared to controls. No explanation was offered for lack of difference between the DU and FD patients[14]. Similarly, the results of a study examining psychosocial variables in organic dyspepsia and IBS, illustrated that the prevalence of formal psychiatric disorder did not differ significantly in both patient groups. The inclusion of chronic treatment resistant patients, who may account for the higher levels of psychopathology seen in other studies, was minimised by use of consecutive general practitioner referrals[15].

In a recent study, investigators sought to characterise relevant psychosocial variables and quality of life in a population of patients with functional dyspepsia, primarily referred from a primary care clinic, and in addition sought to correlate these variables with specific dyspeptic symptoms. It was hypothesised that if dyspeptic symptoms represented the physical manifestations of various aspects of psychological distress, a correlation should be evident between specific symptoms, measures of somatisation (the tendency to express emotional dysphoria as physical symptoms) and specific psychosocial variables. Self-report measures were used to evaluate symptomatology and psychological parameters. Results showed that, compared with healthy patients, patients with FD had significantly greater scores for dyspeptic symptoms, significantly greater psychiatric distress and significantly poorer quality of life. However, symptom severity and psychological distress did not correlate strongly. Thus, because of the lack of correlation, the authors concluded that digestive symptoms at that level of care are unlikely to represent physically manifested emotional distress. Instead, it would appear that dyspeptic symptoms are occurring against a background of psychiatric morbidity[16]. Studies, in addition to demonstrating greater psychiatric co-morbidity, have also revealed a greater tendency towards multiple extra-intestinal somatic complaints in FD patient groups[6]. This, together with overlapping symptoms in the various functional syndromes, contributes to the argument of proponents of a unitary somatisation syndrome[6].

Further studies have lent support to the notion that psychological distress, not necessarily warranting a psychiatric diagnosis, is involved in the causative pathway. Patients with NUD, at a clinic level, report more psychological distress than healthy controls[6,18]. However, a number of studies have demonstrated no psychological differences between people with functional bowel disorders who have not consulted a physician compared to community-based healthy controls[6,18,19]. This has engendered the assertion that psychosocial factors are not implicated in the aetiopathogenesis of FD and IBS, but rather serve to motivate health-care seeking i.e. act as confounding factors. More recently, in contrast to this dogma, elevated levels of psychological distress across all domains (except phobic anxiety) of the SCL-90-R, a measure of psychological state, have been demonstrated in a population-based study of subjects with functional GI disorders inclusive of both
Life events
Life-events are changes in a person’s life that require adjustment and where the demands associated with such events exceed resources available, stress is the result. The association between FD and stress in life has often been suggested, though yet again in a minority of studies, inconsistent results have been reported\(^{20,21}\). Severe life stress has been found immediately before the onset of functional bowel disorders\(^{22}\) and may precede consultation with a general practitioner in dyspepsia sufferers\(^{23}\). It has been suggested however, that there is a lack of community studies that have carefully evaluated whether stress is linked to disease or merely to health-care seeking\(^{24}\).

In a retrospective study using semi-structured interview and a number of psychometric tools, authors looked at the occurrence and perception of life events, personality factors and psychopathology of patients with FD, compared with DU patients and healthy controls. Results demonstrated that patients with FD experienced more life-events than both DU patients and controls. In addition, DU patients experienced more than controls. These findings were accounted for by differences in stressful life-events\(^{25}\). Moreover, the most prevalent types of severe events in all groups were changes in social activity, changes in job situation and illness in the family. Though, evaluation of stress is influenced by psychiatric co-morbidity, and indeed higher psychopathology scores were seen in the FD group, one could also argue conversely that the life-events precipitated the psychopathology. The authors suggest that the difference in perception of life-events may relate to an imbalance between stressors and coping abilities and that this may indirectly mediate gastric motor disturbances and abdominal discomfort. Similar findings were established in a clinic-based study which showed that highly threatening chronic difficulties were significantly more evident in the non-ulcerative dyspepsia group than controls, as were acute life-events which remained highly threatening one week after their onset\(^{26}\).

A population based study, looked at a number of psychosocial variables, life-event stress inclusive, and their association with FGID’s. Using the life experiences survey, it was demonstrated that subjects with higher negative change scores and greater total change scores were more likely to have a FGID. When the comparison was then limited to NUD patients only, subjects with higher positive change scores (indicating change with a positive impact) and higher total change scores were more likely to have NUD. Life-threatening events, in contrast to the latter study, were not associated with NUD\(^{27}\).

Personality and coping style
In one study examining personality, investigators hypothesised that patients with FD would have more nervous symptoms and a different personality pattern than healthy control subjects\(^{28}\). Interesting findings were illustrated. Using a personality inventory, the patient group reported a lower detachment score than the control group, the detachment scale relating to the individual’s need for social distance and coldness in social relations. This finding would indicate a greater need for attachment, which could conceivably lead to frustration. Female patients scored lower socialization and higher suspicion than male controls. The authors suggest their findings may reflect a relationship between personality and development of gastrointestinal symptoms. Higher levels of introversion and suspicion may hinder adequate coping with stress.

Previous personality studies, showed significantly more symptoms of anxiety and tension and higher scores for trait tension and hostility for FD patients compared with peptic ulcer disease patients\(^{18}\). Others would suggest that personality differences are minimised when IBS co-morbidity is excluded. It has been shown that individuals with FD, without IBS, have higher scores of anxiety, neuroticism and depression, than paired community controls, but the differences are relatively small\(^{29}\). Where IBS is an accepted co-morbidity the differences are more significant\(^{30}\). Neuroticism, characterised by an individual’s tendency to have an exaggerated responsiveness to physiological changes, may theoretically exert an influence on the recognition and reporting of symptoms\(^{31}\).

Coping response is another psychological factor that has proposed relations to FD symptoms. With regard to the relationship between coping behaviours and well being, FD patients may adopt a distinct coping pattern that is related to their heightened level of anxiety\(^{32}\). It has been shown that a non-discriminative, action orientated coping pattern was found to be characteristic of FD regardless of stressor controllability. Consistent use of this coping strategy under all circumstances may not be useful in mitigating distress, may provoke anxiety, may not be useful in altering outcome and may prove costly in terms of psychological strain.

Abuse
Studies suggest that abuse, both past and current, is an important risk factor for functional GI symptoms. It has been found that women outpatients with functional, as opposed to organic bowel disease, were nearly twice as likely to report sexual abuse\(^{20}\). Clinic-based studies may carry potential selection bias. However, a population based cross-sectional study, using a self-report questionnaire, has shown that subjects with an abuse history, in childhood or adulthood, were significantly more likely to report a history of dyspepsia or heartburn and that this association could not be explained by confounders for which the analysis accounted\(^{33}\). An interview-based study examining the prevalence of FGID’s in women subject to ongoing abuse revealed that 71% had a FGID-67% having FD. This group also had higher levels of psychological distress\(^{34}\).

These observations do not imply causality and the role of confounding co-morbidities to which the individual may be predisposed by virtue of the abuse, may be an issue\(^{35}\). It has also been observed that there is a high frequency of abuse history in other chronic pain conditions. Abuse may not be implicated in the aetiology of FGID but may be associated with a tendency to communicate psychological distress through physical symptoms\(^{36}\).

Psychosocial factors and health-care seeking
Aetiological issues aside, it is reasonable to hypothesise
that psychosocial factors may also exert their effect in FD through an influence on health-care seeking. Health-care seeking is determined by a plethora of factors including symptom severity, personality, coping skills, social support, sociodemographics, psychological morbidity and health-care availability. Illness behaviour, which may be defined as how one perceives, evaluates and acts upon symptoms, is also critically involved in the decision to seek medical consultation. Intrinsic to this process are illness beliefs and attitudes. It has been suggested that the observed association between FD and psychosocial factors is in fact mediated through increased help-seeking prompted by elevated levels of psychosocial distress. This theory is derived from the findings by some investigators, in volunteer studies, identifying no differences across psychological parameters between healthy controls and FD patients who have not sought medical advice.

A number of studies have demonstrated elevated levels of psychosocial distress amongst consulters recruited at clinic, in comparison with non-consulters, with functional dyspeptic symptoms. One such study showed that the former have more worries about cancer and heart disease than the latter. Consulters interviewed also had experienced more stressful or threatening life-events over the previous 6 months. These are factors that may potentially motivate health-care seeking to ameliorate concern and gain reassurance. More recently, a critical review of the literature pertaining to predictors of health-care seeking for both IBS and FD, was undertaken. Authors concluded that psychosocial factors including life-event stress, psychological morbidity, personality, abuse, and abnormal illness attitudes and beliefs have been found to characterise those that seek help versus those that do not. In a study that sought to examine the differences in behavioural and perceptual characteristics between non-consulters and consulters with FD in a Chinese population, it was found that non-consulters were distinguishable by their perceptual style, coping behaviours and psychological symptoms. Moreover, investigators found levels of anxiety and depression to be highest in consulters compared to non-consulters and healthy controls.

Others refute the generalisability of these findings. The results of a recent community based study suggest that psychosocial factors are significantly associated with functional GI disorders in both consulters and non-consulters, at population level. The debate thus clearly remains unresolved.

**ABNORMALITIES OF FUNCTION IN FUNCTIONAL DYSPPEPSIA**

Though the pathophysiology underlying FD is incompletely elucidated and seems heterogeneous, several mechanisms to explain symptom manifestation have been proposed. Motor abnormalities of the upper gut have been demonstrated including delayed gastric emptying, antroduodenal dysmotility and altered gastric compliance. So too has gastric sensory dysfunction in the form of visceral hypersensitivity. Infective and inflammatory processes have also been proposed which may involve *Helicobacter pylori* and acute gastric infection. Different types of inflammation throughout the gut can leave a legacy resulting in abnormal function in apparently histologically normal organs, by means of proposed mechanisms including: defective resolution of inflammation, changes in mucosal function and persistent changes within the ENS. In a review of the molecular basis of FGIDs, it has been suggested that mediators or regulators of mucosal inflammation, including cytokines, may trigger events that ultimately result in the manifestation of functional gastrointestinal disorders. Abnormalities of receptor function, including central serotonin receptors have also been implicated.

**Influence of psychosocial factors on abnormalities of function**

Using the brain-gut interaction construct, how then do psychosocial factors ultimately influence FD symptomatology? Stress is a characteristic shared by the various psychosocial factors that have a demonstrated association with FD. From a psychological perspective, stress is emergent when demand exceeds resources. More broadly, it is defined as any threat to the homeostasis of an organism, be it real or perceived, which may be posed by events in the outside world or within. In recent times, the biological substrates of the stress response, in health and disease, have been recognised. In brief summary, centrally, interoceptive (systemic) stressors employ subcortical circuits, while exteroceptive (psychological) stressors engage pathways in the limbic forebrain, hippocampus and amygdala. Both circuits activate hypothalamic effector neurons. Corticotrophin releasing hormone (CRH), not only secreted in the hypothalamus, is an important mediator of the central stress response. The latter is generated by a network of integrative brain structures, in particular subregions of the hypothalamus, amygdala and periaqueductual grey. Mayer refers to this central circuitry as the ‘emotional motor system’ (EMS), which is under feedback control via ascending monoaminergic projections and circulating glucocorticoids. Outputs from the EMS play a role in mediating the peripheral response. Neuro-endocrine systems are heavily implicated and include the hypothalamic-pituitary-adrenal (HPA) axis. The autonomic nervous system and endogenous pain modulation system are also involved. It is generally recognised that early life-trauma and chronic severe stress in adulthood can cause long-lasting, potentially irreversible, changes in the stress response system. It is possible therefore that in vulnerable individuals the neurobiological substrates of stress, or maladaptive states thereof, operating on the BGA, form part of the link between psychosocial factors and FD.

Approximately one in three FD patients have a definable gastric motor abnormality. In patients with FD, the effect of stress on antroduodenal activity has been studied, revealing findings contrary to those seen in healthy controls. In an experimental design, it was shown that antroduodenal motility was diminished by stress in healthy controls. This was not the case in dyspeptic patients suggesting that FD may arise from the effect of stress on upper gut motility in susceptible individuals. The autonomic nervous system has been proposed as the
mediating mechanism for this effect. In an earlier study, antral motility and autonomic function in FD patients and healthy controls were investigated\[58\]. The effect of mental stress on antral motility was also examined. Findings confirmed autonomic dysfunction, specifically low vagal tone, in functional GI disorders. At baseline, post-prandial antral motility was on average reduced in FD patients compared to controls. Moreover, acute mental stress diminished post-prandial antral motility in healthy subjects but not in dyspeptics. In fact, some patients demonstrated increased motility. Subsequently, it was proposed that poor vagal tone may represent a mediating mechanism for the causal effects of personality on antral motility and related FD symptoms\[90\]. The relationship among a number of psychological factors, antral dysmotility and dyspeptic symptoms in FD patients were examined. Specifically, it was asked if any such relationship depends on vagal activity, by examining the relationship between these psychological factors and vagal tone. Findings showed that psychological predictors explained a substantial amount of the variance in task-related dyspeptic symptoms, vagal tone and gastric antral dysmotility. FD patients had lower scores on vagal tone and motility index in addition to the expected higher scores on epigastric discomfort. Symptoms appeared to be predicted by trait anxiety, depression and neuroticism and poor vagal tone was associated with neuroticism.

Several studies have established that patients with FD have enhanced sensitivity to gastric distension thus potentially allowing physiological stimuli to induce symptoms\[43,57\]. The mechanisms underlying visceral hypersensitivity are not fully clarified but there are several sources of evidence for a role of the central nervous system. Studies in experimental animals indicate that acute psychological stress seems to facilitate increased sensitivity to visceral stimuli\[40\]. Conceivably, psychosocial stressors may affect visceral sensation through an effect on central processing and/or modulation of afferent visceral information or on central cortisol receptors. With reference to the latter, a thorough characterisation of the HPA axis in FGID has not been reported. However, it has been demonstrated that chronic stress may result in HPA axis overactivity and thus hypercortisolaemia\[42\]. Brain regions involved in visceral sensation, and indeed mood regulation, express cortisol receptors and abnormal levels of cortisol can cause changes in these structures ultimately resulting in abnormal visceral sensation, affective disorders or both\[12,50\]. Imaging research has revealed considerable overlap between brain regions involved in processing visceral sensation and those important for emotional regulation\[12,50,49\]. From animal research, neonatal maternal separation in rats, a model of early-life stress, predisposes them to develop visceral hyperalgesia in response to psychosocial stress\[40\]. It is felt that this is probably CRH mediated.

Approximately 25% of FD cases develop acutely after an acute infectious illness often characterised by vomiting and fever\[48\]. It is well recognised that stress plays a role in immunological modulation\[40\]. Chronic stress renders individuals more vulnerable to intestinal infection and inflammation, which can be an important pathophysiological mechanism in post-infectious FGID\[42\].

**PSYCHOSOCIAL FACTORS AND MANAGEMENT OF FUNCTIONAL DYSPESIA**

The association between psychosocial stressors and FD and the high rates of psychiatric co-morbidity in FD, clearly have implications for effective management. Taking a psychosocial history may help reduce return visits in IBS patients and this may also apply to other FGIDs\[63\]. Depression and anxiety have been shown to adversely affect outcome in IBS\[64\] as have pronounced health worries and poor psychosocial support. Overt psychiatric illness should respond to conventional treatment and if suspected, or if there is evidence of somatisation in other systems leading to multiple consultations across specialties, referral to a mental health profession may be considered\[8\]. As with IBS, treatment in FD is symptom driven. In reducing the likelihood of invalidating the patient’s symptoms (secondary to lack of organic pathology) it may help to explain the mechanisms underlying brain-gut interactions. Acknowledging the relevance of psychosocial factors will no doubt meet with some resistance in certain patients.

If the role of psychosocial factors in FD remains to be fully clarified, then the role of psychological therapies is similarly undetermined. However, patients with FD may benefit from psychological treatments. This is particularly true of those with chronic symptoms unresponsive to conventional medical approaches. Psychotherapy has been defined as an interpersonal process designed to bring about modifications of feelings, cognitions, attitudes and behaviour, which have proved troublesome to the patient seeking help from a trained professional\[40\]. There are wide ranges of interventions that can be described as psychotherapeutic including cognitive-behavioural therapy (CBT), psychodynamic psychotherapy and group therapies. Psychodynamic therapies focus on how maladaptive ideas and behaviours have emerged whereas cognitive behavioural work concentrates on how maladaptive ideas and belief systems are maintained by the patient’s environment and behaviour\[60\].

A systematic review to establish the effectiveness of psychotherapy and hypnosis in FD, revealed a paucity of randomised controlled trials investigating psychological intervention in FD\[60\]. The data available suggest that these techniques benefit FD but the authors conclude that the evidence is insufficient to confirm their efficacy. One particular study randomised patients to psychodynamic-interpersonal psychotherapy or supportive therapy, which consisted of sympathy and support for the same duration of time as the intervention arm. Patients recruited had chronic symptoms and a history of failed response to conventional pharmacological therapy. After 12 wk of treatment the intervention group were significantly better than controls\[12,50\]. CBT has been found to be effective in the treatment of depression, anxiety disorders and of patients with medically unexplained symptoms\[58\]. A study comparing the outcome of cognitive therapy (attempts to change dysfunctional thoughts and behaviour...
by cognitive restructuring, behavioural modelling and role-play) and a control group intervention (bimonthly therapist visits), in patients with FD, demonstrated significantly greater improvement in the former[9].

The rationale for using psychotropic medication rests in the level of psychiatric co-morbidity seen in patients with FD as mentioned earlier. Additionally, there is data to support the use of antidepressants in the relief of chronic pain[8]. A meta-analysis of the treatment of functional gastrointestinal disorders with antidepressant medications, identifying 3 randomised controlled trials evaluating FD, suggested that antidepressants (predominantly tricycles) might reduce the symptoms of FGIDs. Of note, the majority of studies included, used antidepressant doses that are essentially sub-therapeutic for treatment of depression. The authors thus suggest that it is unlikely that the benefit observed is due entirely to the antidepressant effect of these drugs[9]. There is little data available on the use of selective serotonin reuptake inhibitors. It seems reasonable that choice of drug is tailored to the individuals dominant symptom pattern whilst remaining cognisant of side-effect profiles. Essentially, if used, psychotropics should be regarded as complimentary to an overall multi-component plan.

In conclusion, functional dyspepsia is a heterogeneous disorder in which the role of psychosocial factors continues to be the subject of debate. The suggestion that psychological morbidity and social stressors serve to motivate physician consultation, rather than possessing an aetiologic role in symptom pathogenesis, has been challenged. Despite inconsistent findings, it is evident that there is a high level of psychiatric co-morbidity with FD and that anxiety disorders predominate. Individuals with FD appear to experience a greater number of life-events, which are not limited to those of negative impact, compared to healthy controls. A recent or remote history of abuse is a non-specific risk-factor for symptoms of FD. The speculation that functional gastrointestinal disorders and psychopathology share common pathophysiology is interesting and warrants further examination. The evolving appreciation and delineation of brain-gut interactions and CNS processing continues to enhance our understanding of the complex mechanisms underlying symptom generation, interpretation and presentation.

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