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The future of neuroscientific research in functional gastrointestinal disorders: Integration towards multidimensional (visceral) pain endophenotypes?

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Abstract

The growing evidence for a key role of psychophysiological processes in the etiopathogenesis of functional gastrointestinal disorders (FGID) originates from various sources, including epidemiological, psychometric, physiological, and behavioural studies. Functional neuroimaging has improved our knowledge about central processing of visceral pain, a defining feature of FGID. However, results have been disappointingly inconsistent, often due to psychosocial factors not being controlled for. In this paper, we aim to show that using integrated research strategies, encompassing a number of scientific disciplines, is critical to advancing our understanding of FGID. We will illustrate this by describing recent integrative studies that may serve as good examples. More specifically, future FGID neuroimaging studies should control for psychosocial factors and incorporate methods from other branches of neuroscience outside this field, especially cognitive, affective and autonomic neuroscience. We therefore propose a framework for the development of an integrative cross-disciplinary research strategy based on advancing our understanding of visceral nociceptive physiology in health as well as vulnerability and susceptibility factors for FGID. This approach will allow the identification of factors responsible for the inter-individual differences in visceral pain perception and susceptibility to chronic visceral pain, leading to the description of multidimensional (visceral) pain "endophenotypes." These may represent the critical steps needed towards a pathophysiological, rather than symptom-based, classification of FGID, which may be more suitable for genetic association studies. This approach may ultimately culminate in individual tailoring of treatment, in addition to disease prevention, thereby improving outcomes for the patient and researcher alike.
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Introduction

In the United Kingdom, unexplained somatic symptoms are estimated to account for up to 20% of general practitioners' visits [1]. Chronic pain is considered to be a central defining feature of many of the medically unexplained syndromes, including the functional gastrointestinal disorders (FGID). FGID represent a considerable unmet need in modern gastroenterological practice and are currently defined using symptom criteria rather than through a mechanistic understanding of their pathophysiology [2]. FGID are the most frequently occurring diagnostic entity in the gastroenterological out-patient setting and are associated with significant economic burden in terms of work absenteeism, presenteeism and healthcare utilization [3,4]. The intrinsic nature of FGID is as a heterogeneous group of symptom-based disorders, rather than as diseases per se; and these symptoms display considerable interindividual and

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temporal intraindividual variation. Their pathophysiology is likely to be multi-factorial and remains incompletely understood, but an emerging body of evidence has identified the key role of psychophysiological processes in the etiology of these disorders.

Emerging perspectives on the role of psychophysiological processes

Firstly, epidemiological studies indicate that comorbidity with psychiatric disorders (mostly mood and anxiety disorders) as well as prevalence of severe psychosocial stressors [including a history of (childhood) sexual or physical abuse] is high in FGID [5–8]. Recent evidence has shown that this is not only true in tertiary care, but also in primary care [9] and in non-help-seeking community-based populations [6].

Secondly, behavioural research has shown that the hypersensitivity to rectal distension found in irritable bowel syndrome (IBS) patients is often attributable to hypervigilance for visceral stimuli and a greater tendency to label visceral sensation as negative/painful rather than as a normal interoceptive sensation [10]. Furthermore, "somatisation" and to a lesser extent, depression, are more important determinants of symptoms than visceral sensitivity in functional dyspepsia (FD) [11]. Additionally, gastrointestinal (GI) symptom-specific anxiety has been shown to be an important mediator of the relationship between neuroticism or general anxiety on the one hand and IBS diagnostic status or symptom severity on the other [12].

These epidemiological and psychometric/behavioral studies have lead to a biopsychosocial conceptualization of FGID, for example, as formulated by Drossman et al. in the "Rome" international consensus reports on FGID [13]. The biopsychosocial concept of illness, first explicitly formulated by the late George Engel in 1977, postulates that all illnesses, but especially "functional somatic disorders" (FSS), result from complex reciprocal interactions between biological, psychological and social factors [14]. Although this model fails to conceptualize the exact nature of these interactions, it remains, in our opinion, an important psychophysiological framework for explaining the pathophysiology of FGID, both in a clinical and a research context. However, the "neurogastroenterology" academic community has been slow to adopt an integrative biopsychosocial research strategy. In this respect, research into chronic visceral pain has "lagged" behind its somatic counterpart. In addressing this imbalance, the latter part of the 20th century was greeted with great excitement that technological advances in functional neuroimaging techniques would finally herald a new dawn in our understanding of the "visceral pain neuromatrix," in health and in FGID (see, for example, Ref. [15]). However, despite considerable academic and financial investment in functional neuroimaging, its initial promise has not (yet) yielded consistent results that are applicable to patient groups [16]. It is our opinion that this may be due to the fact that both the methodology and results from these imaging studies have not been sufficiently integrated with neither the epidemiological and behavioral evidence on the role of psychophysiological processes outlined above, nor with other branches of neuroscience, especially affective, cognitive, and autonomic neuroscience.

Therefore, to move the field forward, the development of an integrated multidisciplinary research strategy directed to the identification and interaction of vulnerability factors, whether they be genotypic, psychological, or physiological factors, is warranted to explain disease genesis and may ultimately result in disease prevention. Given the high comorbidity between all FSS and the growing evidence for an at least overlapping etiopathogenesis, we may even argue that this integrative approach should be extended beyond the borders of the FGID field to include other functional (pain) disorders such as fibromyalgia and chronic fatigue syndrome.

Lessons from somatic pain research

The somatic pain research community has developed such an integrated strategy and as a result it has made considerable progress into unraveling the complex psychophysiological mechanisms by which emotion (e.g., anxiety) and cognition (e.g., attention) influence the processing and perception of bodily signals, by amplifying them at brain level and/or interfering with descending pain modulation. This knowledge has been born out of the fruitful integration between different scientific disciplines within the somatic pain field over the past decades, including, among others, psychology, psychiatry, anesthesia, and various branches of neuroscience. Such a degree of integration has not been achieved yet within the field of "neurogastroenterology," although it may prove to be the vital step in advancing our understanding of these puzzling and heterogeneous FGID. In striving to achieve this goal, we should utilize newer techniques such as functional neuroimaging and genotyping but not forget "old friends" such as psychometrics, behavioral research, neurophysiology, and autonomic neuroscience and, above all, try to integrate them better. Such an integrative strategy may lead to the discovery of multidimensional (visceral) pain "endophenotypes," which may be a first critical step towards a pathophysiological, rather than symptom-based, classification of these complex disorders that may be more suitable for future genetic association studies.

"Endophenotypes" can be defined as "measurable components unseen by the unaided eye along the pathway between disease and distant genotype" and may be , among others, cognitive or neuro/psychophysiological in nature [17]. They may be particularly useful for classifying and diagnosing multifactorial, polygenic diseases; in this

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