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Editorial comment

The swinging pendulum of oesophageal pain—Away from the centre back towards the periphery again

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1. Introduction

Arguably one of the great continuing controversies in visceral pain research is whether the pathology that leads to chronic symptoms is largely concentrated in the periphery or in central structures. In this issue of the *Scandinavian Journal of Pain*, Frøkjær and coworkers [1] report their findings of a case-control study where they sought to delineate the presence or absence of microstructural changes in the central pain neuromatrix of patients with functional chest pain of presumed oesophageal origin (FCP). Using diffusion tensor imaging, they demonstrated that, in a well-defined cohort of functional chest pain patients in the absence of psychological comorbidity, that there were no differences in white matter microstructure. This suggests that the pathophysiology of FCP, in a select group of patients, lies outside these structures. FCP is characterized by recurrent unexplained midline chest pain. The Rome III diagnostic criteria include at least 3 months of symptoms, with onset at least 6 months prior to diagnosis, in the absence of another cause such as oesophageal dysmotility or gastro-oesophageal reflux disease [2]. Despite this criteria, it remains unclear as to whether disorders with similar symptoms, albeit with contrasting nomenclature such as non-cardiac chest pain (NCCP) or syndrome X, represent identical clinical entities [3]. Notwithstanding significant concomitant reductions in quality of life, patients often have recourse to disproportionately high healthcare utilization, often manifest in recurrent negative investigations across a number of specialties. Moreover, patients with FCP frequently have symptoms that are refractory to standard therapies [4].

2. Pathophysiological mechanisms in functional chest pain

The pathophysiological mechanisms proposed to account for the development and maintenance of chronic symptoms of chest pain in FCP are incompletely understood but have been postulated to be encompassed within a biopsychosocial framework [5]. To date, three mechanisms in particular have been subject to objective evaluation. Firstly, the stress responsive physiological systems, namely the autonomic nervous system and the hypothalamic–pituitary–adrenal axis, act as brain-body nexi and are thus critical components of physiological adaption in response to changes in the external and internal milieu. Dysfunction within both of these systems has been demonstrated in FCP [6]. Secondly, up to 61% of FCP patients display a degree of psychological comorbidity which itself may enhance oesophageal perception possibly through hypervigilance [7]. Whether psychiatric comorbidity is a primary cause, a predisposing factor, a co-morbid illness or indeed a sequelae of FCP, remains to be fully determined. Finally, oesophageal hypersensitivity, defined as enhanced sensitivity to experimental oesophageal stimulation, is widely considered to be a pathophysiological feature of FCP albeit with insufficient receiver operator characteristics to make it useful in the routine clinical setting [8,9]. Nevertheless, this observation has spawned further research suggesting that a combination of an increase in afferent pathway sensitivity, abnormal cortical processing or pain hypervigilance may account for this epiphenomenon [10].

3. Functional neuroimaging in chronic visceral pain disorders – a wasted opportunity or a new hope?

Although accumulating animal evidence has provided important insights into central and peripheral pathways that facilitate visceral nociception, a relative paucity of knowledge of these pathways in humans remains as significant proportion of the current knowledge is derived from somatic pain studies. Therefore, the development of a mechanistic understanding of how the brain processes sensory information from visceral structures remains in its infancy. Whilst pathways involved in the perception of visceral pain are highly complex, they are dynamic and can be modulated in response to internal or external stressors. A wide variety of mechanisms can be engaged in response to stressors from the level of primary afferents to the cerebral cortices. The consequence of these mechanisms is that there is a considerable degree of plasticity within the system. Our understanding of these pathways and mechanisms that contribute to the visceral nociception has advanced

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considerably over last two decades, fuelled, in part, by advances in non-invasive functional neuro-imaging. Indeed, the period from the early 1990s, when these techniques were becoming more widely available, was heralded as a "new dawn" in visceral pain research. Despite this initial promise, functional neuro-imaging has at best contributed supporting evidence for the importance of central structures in visceral pain syndromes and at worst provided conflicting and inconsistent conclusions. Arguably, the cause of this has been the failure of neuroimaging studies to sufficiently control for confounding factors both within healthy subjects and patient groups [11]. Nevertheless, the application of good study design, encompassing the selection of sufficiently homogeneous groups, allied with the utilization of novel validated techniques in image analysis are a source of renewed optimism in the field. Thus, Frøkjær et al. should be lauded for following these principles meticulously.

4. Diffusion tensor imaging in chronic visceral pain

Diffusion tensor imaging (DTI) has become prominent magnetic resonance imaging technique in neuroscience research, generating in excess of 750 publications over the last decade. DTI allows the visualization and characterization of white matter integrity and architecture. As a technique *per se*, DTI is a rapidly evolving technique in terms of its acquisition, image processing, analysis and interpretation. However, similar to all scientific techniques, DTI has intrinsic limitations. For instance, the model is unable to rationalize non-normally distributed diffusion. However, that aside, when combined with functional brain mapping, it provides a comprehensive tool for delineating the functional anatomy of central structures. Recently, DTI has started to be applied to the study of chronic visceral pain syndromes, although in contrast to previous studies where central changes have been demonstrated using where there is organ specific demonstrable pathology, Frøkjær et al. failed to find any microstructural re-organization in the visceral pain neuromatrix. Although their patient sample size was small, it was comparable to other previous studies published in the area, and given the clinical homogeneity of their sample, it is unlikely that there is a significant burden of type II error within this study. Notably, Zhou et al. examined the white-matter microstructural changes in 36 patients with functional dyspepsia using DTI in a case-control design [12]. Patients demonstrated heightened fractional anisotropy, a measure of neuronal organization, in multiple white matter tracts including areas known to be important for visceral pain processing; internal capsule, posterior thalamic radiation and corpus callosum. However, when the co-variants of anxiety and depression were controlled for, these between group differences were largely lost. Therefore, it is a plausible proposal that the white matter changes observed in patients could be a sequelae of elevated levels of psychosocial distress. Moreover, a recent meta-analysis of DTI in major depressive disorders reported that decreased fractional anisotropy in the white matter fascicles connecting the prefrontal cortex within cortical and subcortical areas was a consistent finding amongst studies [13]. Given that specific exclusion criteria of FCP patients were psychiatric comorbidity and anti-depressants in this study, it is likely that such changes were controlled for thereby allowing us to make a more definitive conclusion regarding the absence of white matter reorganization in FCP.

5. Functional chest pain – a heterogenous disorder?

As in many functional gastrointestinal disorders, FCP has a number of pathophysiological facets. Whilst a number of studies have hitherto examined many of these psychophysiological facets in isolation, the adoption of such a reductionist approach has constrained our wider understanding of their co-relationships. In many respects, FCP remains a diagnosis of exclusion, which sadly for patients is often never formally made, or when it is, at the end of an exhaustive series of invasive investigations. It is possible that within the diagnostic umbrella of FCP, there are a number of distinct clinical phenotypes reflecting differential locations of altered pain processing. Hobson et al. demonstrated three phenotypic subsets of NCCP patients based on sensory responsiveness and objective neurophysiologic profiles of evoked potentials to electrical oesophageal stimulation [14]. We have sought to extend these findings and have recently reported, in a cohort defined in a manner similar to Frøkjær et al., two distinct sub-populations of FCP based on their psychophysiological responses to visceral and somatic pain [6]. The first of these, accounting for approximately 70% of patients, were characterized by high neuroticism, trait anxiety, baseline cortisol, pain hypersensitivity, and parasympathetic response to pain. In contrast the second group, comprising approximately 30% of patients, had the converse profile. It is possible that these phenotypic stratifications in future brain imaging studies may enhance homogeneity of participants but also potentially lead to the individualization of treatment in the clinical environment.

6. So where does this leave the field moving ahead?

Whilst negative studies may not seem at first glance to be attractive or interesting, particularly in functional neuroimaging, in fact they often provide more important mechanistic understandings than positive studies. Indeed we would vigorously argue that within the field of visceral pain research that such positive studies are often over-interpreted leading to erroneous inferences being made. With respect to this study, we have to refer back to the original hypothesis that the authors posed of whether white matter reorganization is present in FCP. The likely answer, in well-defined groups in the absence of psychological comorbidity, is that it is not. This is not to mean that central abnormalities do not exist in FCP patients, but may allow efforts at refining therapeutic interventions focussing on peripheral targets.

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