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The common link between functional somatic syndromes may be central sensitisation

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ABSTRACT

Objectives: Functional somatic syndromes are common and disabling conditions that all include chronic pain, and which may be related to central nervous system sensitisation. Here, we address the concept of central sensitisation as a physiological basis for the functional somatic syndromes.
Methods: A narrative review of the current literature on central sensitisation and physiological studies in the functional somatic syndromes.
Results: Central sensitisation may be a common neurophysiological process that is able to explain non-painful as well as painful symptoms in these disorders. Furthermore, central sensitisation may represent an endophenotypic vulnerability to the development of these syndromes that potentially explains why they cluster together.
Conclusions: Further research is needed to verify these findings, including prospective studies and the standardisation of combined methods of investigation in the study of central sensitisation in functional somatic syndromes. In turn, this may lead to new explanatory mechanisms and treatments being evaluated. Our conclusions add to the debate over the nomenclature of these syndromes but importantly also provide an explanation for our patients.

Introduction

Functional somatic syndromes (FSS) are conditions in which physical symptoms are not fully explained by an established, alternative medical disorder (Table 1). FSS are common, disabling, and incur a significant use of health care resources and are a source of financial burden borne by patients, their families and society [1,2]. The conceptualisation of these disorders as being 'unexplained' is not only a potential barrier to improved care [3], but it is also challenged by our increasing understanding of them from a neurophysiological perspective.

Multiple and separate, or single and together?

The nosology of FSS is undetermined. This is in part due to uncertainty regarding both pathophysiology and aetiology as reflected in the DSM V review of the classification of somatic syndromes [4] and the borderland between mental and physical health that they inhabit [5]. FSS encompass a wide range of apparently distinct syndromes (Table 1). However, symptoms overlap between the disorders to such an extent that some have suggested that there is one generic FSS, rather than many [6], whilst others have proposed that FSS are discrete disorders, grouped together by common symptoms, but separated by individual pathophysiologies [6]. These opposing arguments have led to the coloquialised question as to whether we should 'lump' these disorders together, or 'split' them apart [6,7].

Patients with one FSS are more likely to also suffer from another [8]. For example 51% of patients with chronic fatigue syndrome (CFS) and 49% of patient with fibromyalgia (FM) also have irritable bowel syndrome (IBS) [9]. This may be because these disorders seem to share common predisposing risk factors (but not precipitants) [10,11]. These cited studies examined patients with either IBS or CFS and reported predisposing factors common to both conditions (other FSS and mood disorders), in addition to precipitating factors that differentiated them (different infectious agents) [10,11].

Chronic pain and the functional somatic syndromes

Research into the pathophysiological mechanisms of FSS is made difficult by the nature of these disorders, which represent symptom clusters across a wide array of different systems. One approach has been to look at the individual symptoms that predominate in a given FSS, e.g. fatigue in CFS or bowel symptoms in IBS. These symptoms generally involve a combination of different physiological, cognitive and affective drivers, representing an interaction between the central nervous system (CNS) and the dominant system to which the defining

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Table 1
Examples of functional somatic syndromes.

- Irritable bowel syndrome
- Fibromyalgia
- Chronic fatigue syndrome
- Temporomandibular joint disorder
- Idiopathic lower back pain
- Multiple chemical sensitivity
- Tension-type headaches
- Interstitial cystitis
- Chronic pelvic pain
- Myofascial pain syndrome

symptoms are attributed. Defining and then modelling diffuse symptoms such as fatigue is particularly difficult. Pain, on the other hand, represents an easier target. It is a diagnostic criterion of all FSS and the commonest symptom overall [12]. As such, it represents a unifying symptom, a better understanding of which may improve our understanding of FSS as a whole. To this end, some authors have considered these syndromes together as disorders that reflect a state of CNS mediated hypersensitivity to painful stimuli [13,14] — 'central sensitisation' (CS).

Chronic pain and central sensitisation

Pain represents an experience that is influenced not only by sensation, but also by context and prior experience. The experience of pain is distinct from nociception [15]: nociception describes afferent neural activity transmitting sensory information about stimuli that have the potential to cause tissue damage [16], whereas pain is an emergent phenomenon, a conscious experience that requires cortical activity [17], and which can occur in the absence of nociception. Acute pain originates from nociceptors, activating two types of nerve fibre (low threshold fast A delta fibres and high threshold slow unmyelinated C fibres). These fibres synapse onto both wide dynamic range (those that are responsive to all sensory modalities and to a broad range stimulus intensity) and high-threshold neurons in the dorsal horn of the spinal cord, depending on the nature of the painful stimulus encountered.

The superficial dorsal horn is comprised of lamina I and II. Lamina I plays a key role in the modulation of pain transmission with 85% of its neurons being nociceptive with a high threshold for excitation, whilst only 15% have a wide dynamic range, responding to lower thresholds. In comparison, the majority of neurons in lamina V, located in the neck of the dorsal horn, also have a wide dynamic range, and so are predominantly non-nociceptive. Neurons from lamina II terminate locally within the dorsal horn, whilst those from lamina I have long axons that travel in the parabrachial pathway [18]. This pathway along with the spinothalamic tract, carries information to the parabrachial area in the midbrain from where it projects to higher cortical centres, including the hypothalamus, the amygdala and parts of the thalamus [19]. These higher centres form part of a non-specific network of structures previously referred to as a 'neuromatrix' [20] that is thought to be involved in, but not specific to the perception of pain [21]. The different structures within this network contribute to the evaluative, affective and sensory interpretation of the painful stimuli. The parabrachial pathway also projects to other centres involved in the descending control of pain, including the rostro-ventral medulla and the periaqueductal grey area [22]. These descending control mechanisms are responsible for a reduction in the sensation of pain and the inhibition of its spread upon the perception of pain (see Fig. 1a).

Pain perception exhibits neuroplasticity, whereby repeated nociception may result in either habituation (reduced response) or sensitisation (increased response). As such, continued stimulation may result in increased neuronal responsivity or sensitisation [23], depending on the intensity and temporal features of the stimulation. CS refers to a 'pain phenotype' generated by processes that result in the amplification of the pain, which are thought to underlie many chronic pain states. This sensitised state involves both spinal mechanisms, at the level of the dorsal horn and below and supraspinal mechanisms that involve the disproportionately augmented response of a network of higher brain centres [20], with the latter subsequently contributing to the descending control of afferent spinal neurotransmission. CS therefore involves a dual process of spinal sensitisation and augmentation of this neural network. It is important to note, however that these processes occur in parallel rather than in series and that

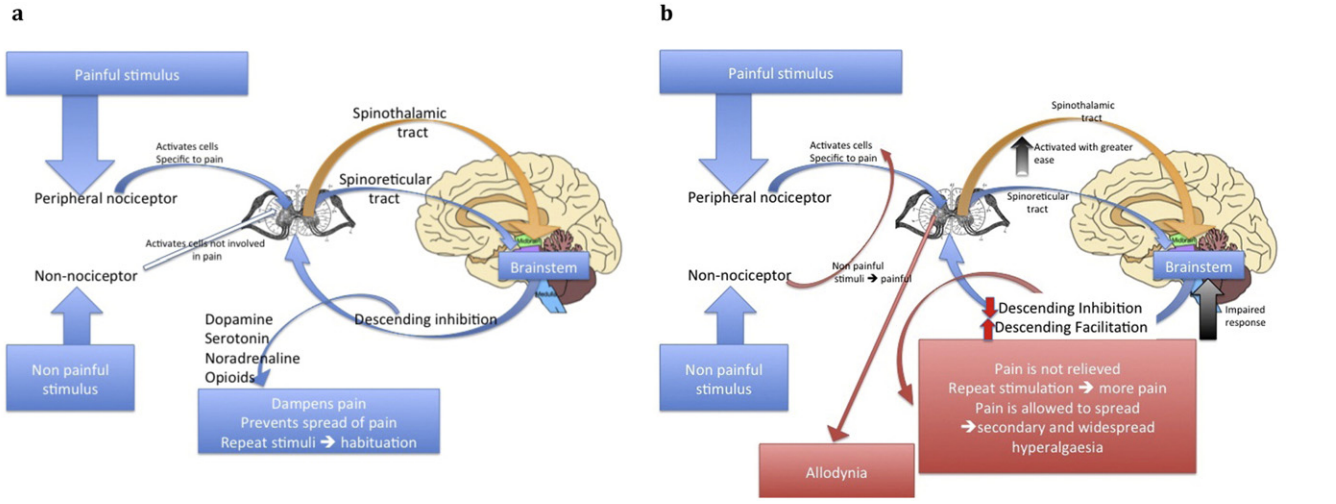

Fig. 1. a&b: Spinal sensitisation: Ascending and descending mechanisms involved in pain control. a: A painful stimulus is able to activate peripheral nociceptors that in turn activate nociceptive neurons in the superficial dorsal horn of the spinal cord. Lamina II neurons project in the spinoreticular and spinothalamic tracts to the brainstem and higher cortical centres. At the level of the brainstem, descending inhibitory mechanisms are activated involving monoamine and opioid neurotransmitter systems (conditioned pain modulation) in tandem with a reduction in descending facilitatory mechanisms. In turn these act to reduce pain and prevent its spread to neighbouring areas. With this system intact, upon repeat stimulation a habituation response is facilitated, whereby the same stimulus intensity results in the same or less painful sensation. b: In a sensitised state, non-painful stimuli are able to activate nociceptive specific dorsal horn cells. A clinical consequence of this is the experience of pain on non-painful stimulation — allodynia. This in turn results in greater activity in ascending pathways to the brainstem. There is a reduced response in descending inhibitory pathways, combined with an increased or no change in response in descending facilitatory pathways, such as that more pain related activity ascends but without a compensatory rise in descending pain inhibition or decline in pain facilitation. This is clinically detectable as increased pain sensitivity and widespread hyperalgesia.