Central Sensitivity Syndromes: Might Recent Advances in Neuroinflammatory Biomarkers Lead to a (Painfully Slow) Change in Perspective?

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BACKGROUND

- **Historically, a lack of suitable disease-defining biological markers coupled with poorly understood underlying pathophysiology has led to unexplained phenomena being explained as "psychogenic" or "functional"**
- **Examples of conditions in this category, sometimes labeled *central sensitivity syndromes*, include chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, and interstitial cystitis**
- **Fibromyalgia (FM) is characterized by widespread chronic pain that is present in all four quadrants of the body and of least three months' duration**
- **In 1990 the American College of Rheumatology (ACR) came out with their first set of diagnostic criteria for FM and have since released updates of in 2010 and 2016, the most recent of which are in the table below:**

Table 1. American College of Rheumatology Fibromyalgia criteria – 2016 revision (Wolfe et al.)

Criteria
A patient satisfies modified 2016 fibromyalgia criteria if the following 3 conditions are met:
(1) Widespread pain index (WPI) ≥ 7 and symptom severity scale (SSS) score ≥ 5 OR WPI of 4–6 and SSS score ≥ 9.
(2) Generalized pain, defined as pain in at least 4 of 5 regions, must be present. Jaw, chest, and abdominal pain are not included in generalized pain definition.
(3) Symptoms have been generally present for at least 3 months.
(4) A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses.

- **Chronic psychosocial stressors and neuroinflammation lead to chronic pain and fatigue, two cardinal symptoms of FM**
- **The inflammatory response is primarily mediated by pro-inflammatory cytokines and chemokines leading to activation of/release from microglial cells**

METHODS

- **Through a qualitative review of the literature and use of fibromyalgia as an example condition, we will illustrate the role of neuroinflammation in pain and propose how it might transform our understanding of the nature of central sensitivity syndromes as a whole.**

NEUROINFLAMMATION

- **Neuroinflammation concerns specialized immune cells, microglia and astrocytes, and specialized endothelium, the blood brain barrier (BBB).**
- **Inflammatory signaling molecules such as cytokines can affect BBB permeability and activate microglial and astrocytes**
- **Microglia express cytokines and cytokine receptors**
- **Microglia are also involved in specialized brain functions including neuronal apoptosis, synapse formation and elimination, circuit plasticity, and complex behaviors**
- **Chronic microglial activation thereby leads to dysfunction of synapses and homeostasis, increased cytokine levels and neurotoxins**

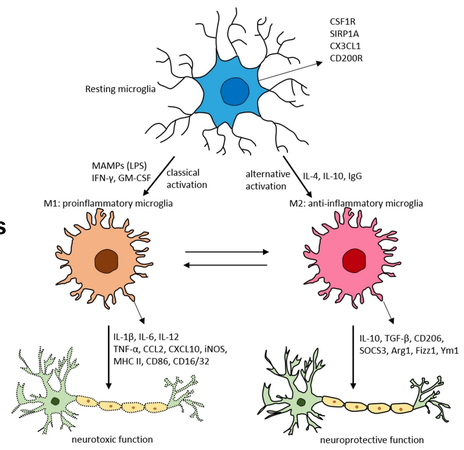

Figure 1. Adapted from Subramaniam and Federoff, 2017.

- **Uçeyler et al. (2011) performed a systematic review and meta-analysis of reported studies measuring cytokine levels and fibromyalgia. Overall, they reported better quality studies showed elevated serum pro-inflammatory cytokines (IL-8, IL-6), and reduced anti-inflammatory cytokines (IL-4, IL-10) in FM patients compared to controls**
- **In a review of literature by Littlejohn (2015) demonstrated increased levels of proinflammatory cytokines in serum (TNF, IL-6) and in cerebrospinal fluid (IL-1β, IL-6), and reduced levels of anti-inflammatory cytokines (IL-4, IL-10) in patients with central pain regional syndrome**

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Proposed Pathophysiology – Neuroinflammation

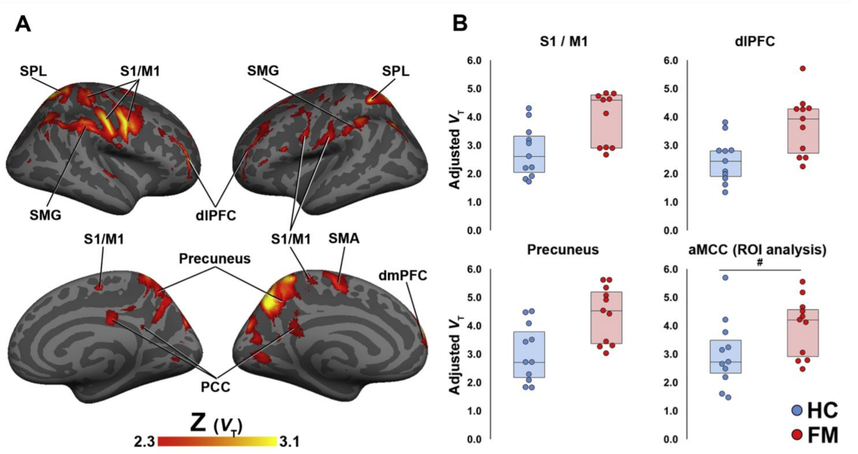

Figure 2. From Albrecht et al., 2019; *A*: Surface projection maps displaying areas with significantly elevated [^{11}C]PBR28 V_T in FM patients compared to controls (FM – n = 11; HC – n = 11) in voxelwise analyses (KI-only sample). *B*: Average ± standard deviation V_T extracted from several regions.

- **As depicted in the figure at left, Albrecht et al. (2019) demonstrated that microglial activation (via PET scan using proteins such as [11C]PBR28) was upregulated in several brain regions (dlPFC, dmPFC, S1/M1, PCC, SMA, SMG, SPL) in FM patients as compared to healthy controls (HC).**
- **They also reported positive association between protein PET signals in several regions and subjective ratings of fatigue.**
- **SPL – superior parietal lobule, S1 – primary somatosensory cortex, M1 – primary motor cortex, SMG – supramarginal gyrus, dlPFC – dorsolateral prefrontal cortex, SMA – supplementary motor area, PCC – posterior cingulate cortex, dmPFC – dorsomedial prefrontal cortex.**
- **Connection between neuroinflammation and pain may be related to chemokines, specifically the CXL which are expressed by neurons and glial cells and initiate cytokine activations leading to neuroinflammation. One of the proteins found to be significantly elevated in both CSF and plasma is the chemokine CX3CL1 (also known as fractalkine) which is linked to the signaling pathway supposed to be most prominent in experimental models of neuropathic pain. Fractalkine is released from primary afferent terminals by cathepsin S. Activated microglia release cathepsin S which then cleaves fractalkine from neurons. If fractalkine is increased in CSF and plasma in FM patients, it could mean an increase in cathepsin S and indicate microglia activation. Increased levels of cathepsin S and/or fractalkine may provide contributions to etiology of pain in FM patients.**

TREATMENT TARGETS

- **Proposed mechanisms of action: 5HT1B/D, 5HT2A, 5HT3, NE mediated Alpha 1/Alpha 2, GABA, Glutamate/NMDA, COMT, REM Sleep regulation, Oxidative Stress, decreased Catalase and Coenzyme Q10.**

	PAIN	FATIGUE	SLEEP	DEPRESSION
Amitriptyline (5HT; NE/α-1/α-2;Ach; H1; NMDA/Glut)	+	+	+	+
SNRI (5HT; NE/α-1/α-2)	+	-	?	+
SSRI (5HT)				+
Pregabalin/Gabapentin (α2δ Voltage gated Ca channel; NMDA/Glut)	+	-	+	-
Cannabinoids (NMDA/Glut)	+	-	+	-
Sodium Oxybate	-	+	+	-
Exercise (aerobic/yoga/ tai-chi/ qigong)	+	?	+	?

DISCUSSION

- **Identification of neuroinflammatory biomarkers in central sensitivity syndromes leads to a more robust understanding of the etiology of these conditions as opposed to the oversimplified conceptualization as "psychogenic" or "functional"**
- **Specific therapeutic targets are identified raising the possibility of novel treatments for these often refractory conditions. For instance, modulating microglial activity may be a possible therapeutic niche in fibromyalgia and potentially other centrally-mediated pain syndromes (Duque et al., 2019).**
- **From an evolutionary standpoint, neuroinflammation and a so-called "trigger-happy" response to painful stimuli and other stressors were advantageous for our ancestors existing in a time of acute threats and infectious disease (Miller, 2016). As our environment changed to one in which more chronic forms of psychosocial stress and non-communicable diseases were prevalent, this sensitive neuroinflammatory response has become increasingly maladaptive (Miller, 2016).**
- **Neuroinflammation impacts selectively vulnerable brain regions, dysregulating release of neurotransmitters (GABA, Glutamate, Ach, H1, Orexin, melatonin, Dopa, NE, 5HT) involved in pain, mood, sleep, fatigue, cognition (Saper and Breder, 1994). Current treatment targets these disordered pathways while also attempting to reduce neuroinflammation.**
- **Further studies are needed to more fully understand the role of neuroinflammation in these conditions.**