SCIENTIFIC COMMENTARY

# Understanding sensory abnormalities in fibromyalgia through autoantibodies

**This scientific commentary refers to 'Aβ low threshold mechanoreceptors contribute to sensory abnormalities in fibromyalgia' by Israel *et al.* (https://doi.org/10.1093/brain/awaf321).**

Fibromyalgia remains a challenging and complex condition, characterised by widespread pain, sensory hypersensitivities, and a range of associated symptoms. Initial studies focused on central nervous system mechanisms as the primary driver; however it is now accepted that peripheral nerve dysfunction also plays a critical role, with 40–50% of patients having small fibre pathology.[1]

More recently, evidence has emerged suggesting that immune mechanisms may contribute to fibromyalgia through the action of autoantibodies.[2] Transfer of immunoglobulin G (IgG) from patients to mice recapitulates fibromyalgia-like symptoms, including heightened sensitivity to mechanical and cold stimuli, along with fatigue-like behaviours. These autoantibodies target the peripheral nervous system, particularly structures within the dorsal root ganglia (DRG)—such as neurons and satellite glia—and the pattern and intensity of patient IgG binding correlates with sensory symptoms and their severity.[3,4] In parallel, sensory neurons display functional changes, with nociceptors becoming hyperexcitable in mice treated with patient IgG.[2] Given that current therapies for fibromyalgia remain largely ineffective, there is a pressing need to better understand the pathophysiological mechanisms linking nervous system dysfunction and sensory abnormalities. Recognition of autoantibody

involvement represents a shift in our understanding of fibromyalgia aetiology and offers a powerful platform to gain mechanistic insight through preclinical models.

In this issue of *Brain*, Israel and co-workers[5] add a novel and technically sophisticated dimension to the evolving picture that is fibromyalgia. Their study integrates clinical data, patient microneurography, and the transfer of patient IgG to mouse models to investigate large-diameter Aβ mechanoreceptor function. Motivated by patient reports of unpleasant sensations such as 'pins and needles', tingling and numbness (paraesthesia and dysesthesia), and pain upon light touch and cooling, the authors analysed questionnaire data from an established patient cohort. They confirmed that these sensory abnormalities are significant symptoms and correlate positively with overall disease severity. Ambient temperature is thought to influence fibromyalgia symptoms,[6] and the authors found that over 80% of patients reported this phenomenon with the majority expressing a preference for warmer temperatures. Since paraesthesia, dysesthesia and allodynia can relate to large fibre function, these findings suggest a plausible contribution of such fibres to fibromyalgia, possibly linked to temperature sensitivity.

Building on these observations and their previous findings that patient IgG can induce mechanical and cold hypersensitivity, the authors hypothesised that autoantibodies may also contribute to increased sensitivity to touch. To test this, they used the passive transfer method, purifying IgG from patients and injecting it into naive mice to assess its ability to reproduce clinical symptoms. Although such experiments are typically short-term (being limited by access to patient samples) and do not replicate the longer exposures experienced by patients, this approach does provide a direct, translational means of assessing IgG pathogenicity. Using IgG from three patients who described increased sensitivity to light touch and subjective symptom improvement following plasma exchange (which removes

>80% of circulating antibodies), they showed that mice treated with these samples developed significant hypersensitivity to light touch when compared with controls.

To determine whether these behavioural changes were mediated by Aβ fibres, the authors employed the *ex vivo* skin–nerve preparation. Here, the skin and peripheral nerve are isolated from the nervous system, enabling direct measurement of nerve activity in response to the application of natural stimuli (e.g. temperature, mechanical forces) to sensory endings. In mice treated with fibromyalgia patient IgG, Aβ fibres—which are largely responsible for tactile discrimination and touch—were sensitised. Specifically, rapidly adapting fibres (Aβ RA) displayed reduced mechanical thresholds, while both Aβ RA and slowly adapting (Aβ SA) fibres showed increased peak firing rates.

Since patients described sensations of tingling, “buzzing”, or “pins and needles” on exposure to cold, the authors also examined cold sensitivity. While their previous work had demonstrated that fibromyalgia IgG can increase the number of C-fibres that respond to cold stimuli,[2] cold sensitivity of large Aβ fibres had not been investigated. Unexpectedly, the authors found that a subset of Aβ SA fibres—normally minimally responsive to cold—acquired cold sensitivity following IgG treatment. These observations are supported by recent findings showing binding of fibromyalgia IgG to large NF200-positive neurons in rodent DRG sections, particularly IgG from patients with prominent paraesthesia.[3]

Further evidence came from *in vivo* calcium imaging of DRG neurons during hind-paw stimulation. Mice treated with fibromyalgia IgG showed increased cold responses in large-diameter neurons, but not in small-diameter neurons, in contrast to previous findings.[2] This suggests heterogeneity in IgG pathogenicity across fibromyalgia patient groups. Medium-sized neurons (likely Aδ neurons) also showed increased responses. Given that

subpopulations of Aδ fibres can convey cold as well as mechanical sensation,[7] further work is needed to ascertain their contribution to fibromyalgia and associated sensory abnormalities.

This study was greatly strengthened by the use of microneurography to conduct neurophysiological recordings in patients. This technique involves inserting a fine tungsten electrode into a peripheral nerve to record the activity of single sensory axons in awake human participants. It is the only technique capable of capturing action potentials from intact human nerves *in vivo*, but its technical challenges are considerable. Israel and colleagues obtained recordings from 29 Aβ SA afferents across 8 individuals diagnosed with fibromyalgia and 12 healthy controls: a significant achievement given the expertise required, although the relatively modest number of units means that care is warranted when attempting to generalise these findings.

Aβ SA fibres were first characterised by their mechanical thresholds and then assessed for responsiveness to controlled cooling ramps. Fibres were classified as cold-sensitive if they fired at least two action potentials during dynamic cooling, or if spontaneously active units increased their firing rate by at least 20%. Such classification is relatively straightforward against a silent background, but becomes technically challenging in fibres with high baseline activity, where more subtle effects may be masked. Moreover, repeated stimulation, particularly with cold, carries the risk of sensitisation or fatigue, factors that are difficult to control in smaller datasets. Nevertheless, a substantially larger proportion of Aβ SA fibres in fibromyalgia patients responded to cooling compared with controls. This is of immediate clinical interest, given patient reports of dysesthesia and paraesthesia in response to cold. Notably, however, the mechanical responsiveness of these fibres was diminished. This is in contrast to the mouse model, where patient IgG increased the mechanical sensitivity of Aβ fibres. Such divergence may reflect species differences, differences in exposure duration

(three days of IgG in mice versus years of disease in humans), or methodological differences in measurement.

These results raise important mechanistic questions. Large-diameter Aβ fibres are not generally thought to express canonical cold-transduction channels such as TRPM8 or TRPA1, and transcriptomic studies support this absence.[8,9] How, then, do these fibres acquire cold sensitivity in fibromyalgia? Possibilities include antibody-mediated modulation of ion channel repertoires, indirect effects via satellite glial cells or surrounding tissue, or long-term reweighting of sensory processing pathways. At present, the exact ionic or molecular mechanisms remain unresolved, and further work is required to clarify how IgG antibodies reshape Aβ function.

Placed in the wider context of fibromyalgia research, this study broadens the field's perspective. While recent attention has centred on nociceptor sensitisation, C-fibre hyperexcitability, and small-fibre pathology, the current findings indicate that large fibres may also be involved. This suggests a more distributed sensory dysfunction that is not confined to one fibre class and may explain why patients experience not only pain but also a spectrum of sensory abnormalities. Evidence for the role of autoantibodies in fibromyalgia continues to grow, and progress will depend on identifying the specific target antigens, particularly as these factors may not underlie symptoms in all patients.[3,10] Nevertheless, the findings of Israel *et al.* lend additional weight to the case for autoantibody involvement and highlight the power of combining basic science with patient-derived samples to advance understanding of fibromyalgia pathophysiology.

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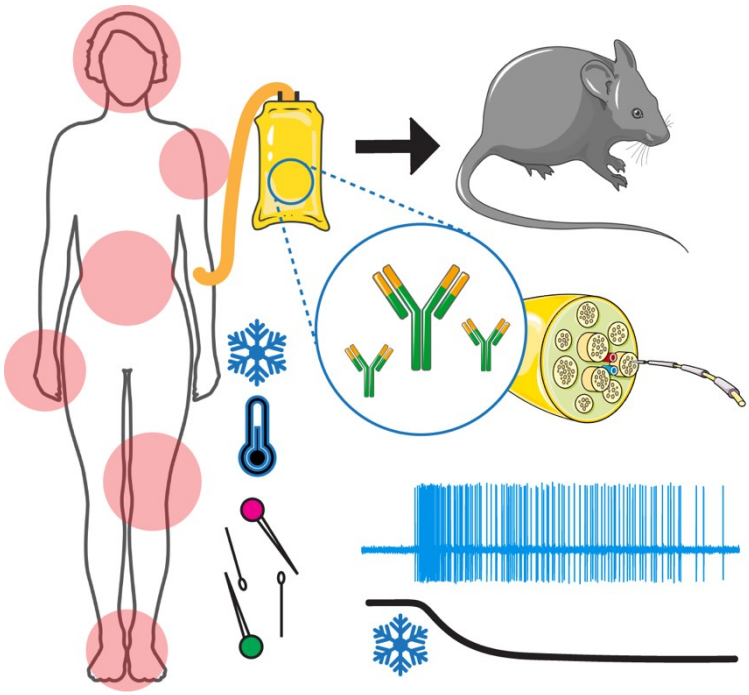

***Figure: People living with Fibromyalgia experience sensory abnormalities, including 'pins and needles' and sensitivity to cold. Passive transfer of patient IgG into mice can reproduce these sensory changes. In both humans and mice, large Aβ fibres exhibit altered responses to cold and mechanical stimuli, which contributes to the spectrum of sensory abnormalities experienced by patients.***

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## Competing interests

The authors report no competing interests.