

progressive multiple sclerosis from the MS Trust survey which the committee accepted. Initially, the company decreased utility in each EDSS state for upper limb dysfunction and clinically meaningful fatigue. The committee noted that these symptoms were among 17 exploratory ORATORIO end points, knew of regulatory principles which deem results only from planned analyses to be confirmatory, knew that appraisals for relapsing remitting multiple sclerosis had not used symptom-specific utility decrements, and heard from the clinical experts that upper limb dysfunction and fatigue are equally important for people with relapsing remitting multiple sclerosis.

The committee considered the company's third version of its cost-effectiveness estimates of ocrelizumab compared with best supportive care incorporating an updated (confidential) commercial arrangement. The company's revised model included a treatment effect diminishing from 7 or from 10 years, and the committee's preferred assumptions: costs, disutilities and a treatment effect associated with relapses; the risk of PML; CDP-24 to estimate treatment effect; data from ORATORIO's double-blind period to estimate treatment effect; and no separate disutilities for fatigue and upper limb dysfunction. The committee acknowledged remaining uncertainties related to the long-term

effect and treatment duration, and discussed unmet need. It concluded that ocrelizumab, with the commercial arrangement, was clinically effective and cost effective for treating early primary progressive multiple sclerosis with imaging features characteristic of inflammatory activity in adults.

We declare no competing interests.

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Insight

The neurology of the Cuban "sonic attacks"

Allegations of "sonic attacks" on 21 US embassy staff members in Cuba first made headlines in 2017. Embassy personnel described hearing intense, mostly high-pitched sounds, often combined with pressure-like or vibratory sensations, and experiencing persistent neurological symptoms afterwards. Speculations about the origin of these symptoms have ranged from clandestine operations to mass hysteria. The medical debate about the nature of the ensuing neurological disorder has been similarly polarised.

The symptoms should be familiar to every neurologist: headache, poor concentration and memory, dizziness, eye strain, tinnitus, sleep disturbance, etc. This set of symptoms can sometimes develop following a concussion, and a report concluded that some form of mild brain injury must have been inflicted. Others have suggested that mass psychogenic illness is a more probable cause of unexplained neurological symptoms in a close-knit social group. Neither hypothesis—brain damage or mass hysteria—is sufficiently supported by clinical evidence. Another hypothesis is that the symptoms correspond to a chronic functional disorder following acute sensory discomfort. Our prime motivation for making this point is not our confidence in having the right diagnosis (we have not seen the patients), but rather our concern at the widespread misunderstanding of functional disorders in the medical community. Functional neurological disorders are very common, accounting for about one in every six new neurology referrals. They comprise a range of disabling conditions with clinical signs

that seem incongruent with pathophysiological disease. But purely psychological models for functional disorders have given way to models that integrate psychological and neuroscience perspectives. Alterations in brain functioning are precipitated by unpleasant sensory experiences, which are distorted through overly precise attention and symptom expectations. Psychological factors of underlying trauma might increase individual risk but, much like smoking for risk of stroke, these factors are not essential to the diagnosis.

The functional disorder persistent postural-perceptual dizziness (PPPD) is the second most common cause of dizziness seen in tertiary centres. It usually develops after an acute vestibular disorder, but can also be triggered by a panic attack or mild head injury. Acute dizziness, of any cause, prompts automatic changes in balance control, such as stiffening of gait and increased body awareness. Dizziness can then persist in a cycle of maladaptation. PPPD has characteristic diagnostic features, including typical exacerbating factors of upright posture, active or passive motion, and exposure to moving or complex visual stimuli, which seem reminiscent of the brief description of dizziness in the embassy personnel: "symptoms were exacerbated by walking quickly, tasks involving head movements, complex visual environments, or in some cases while simply standing still." Of note, PPPD has no psychological diagnostic requirements.

The embassy workers also reported headache, light-sensitivity, and sleep disturbances, as well as cognitive



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For the **original report on "sonic attacks"** see *JAMA* 2018; **319**: 1125–33

For **further discussion on the origin of symptoms** see *JAMA* 2018; **320**: 602–3

For an **update on functional neurological disorders** see *JAMA Neurol* 2018; **75**: 1132–41

For a **review of persistent postural-perceptual dizziness** see *Pract Neurol* 2018; **18**: 5–13

For more on **functional disorders** see Hallett M, Stone J, Carson A, eds. *Functional Neurologic Disorders*. Oxford, UK: Elsevier, 2016



symptoms including impaired concentration and feeling 'mentally foggy', with day-to-day variability and worsening after exercise. This set of deficits, characterised by distractibility and attentional lapses, is also seen in patients with functional neurological disorders. Their symptoms increased over time. This temporal pattern of worsening and spreading of symptoms is not consistent with brain injury, but is typical of chronic functional disorders. The same is true for the reported day-to-day variability of symptoms. However, the investigators dismissed a functional disorder diagnosis on the basis that patients passed tests of effort and were keen to return to work. This reasoning betrays a troubling conflation of functional disorders with malingering. The implication that patients with functional disorders are work-shy is not supported by evidence.

On the other side of the argument, functional disorders have been wrongly equated with mass psychogenic illness. Functional disorders can be shaped by illness beliefs, and they may spread among predisposed individuals within social networks or after alarmist publicity. And yet, we should resist labelling them mass hysteria or mass psychogenic illness. For the US embassy personnel, mass hysteria insinuates that mainly anxiety and mimicry are at work. In contrast, the symptoms of disorders such as PPPD reflect physiological maladaptation that might be shaped but are not caused by social factors. The symptoms are triggered by a pathophysiological event, even if their presentation can be influenced by cultural or personal-illness narratives.

Another functional disorder that exemplifies this interplay between a sensory trigger and secondary maladaptation is acoustic shock, first described in professional telephone operators. After being startled by a loud and unexpected noise, these patients develop persistent otological symptoms such as sound sensitivity, tinnitus, and ear discomfort, often combined with headache, neck stiffness, and disturbances of mood, memory, and sleep. These symptoms evolve, persist, and fluctuate. Tellingly, the onset of acoustic shock is location-bound, with some workplaces having a prevalence of 22%, while others that use the same telephone equipment have no occurrences at all, suggesting an important role of social priming. Similarly, wind turbine syndrome, a controversial illness attributed to faint acoustic stimuli with a constellation of symptoms (dizziness, tinnitus, earache, nausea, and problems with concentration, memory, sleep, and mood) is associated more closely with patterns of media reports than with the geographical proximity of wind turbines.

The way in which the Cuban 'sonic attacks' have played out in public and scientific debate reminds us of similar debates that have been going on since the 19th century in relation to conditions such as railway spine (back pain and secondary neurological symptoms after train accidents) or shell shock (initially thought to be related to brain injury). Typically, the contrast is between something organic and therefore genuine versus something psychogenic with moral overtones of malingering. The idea that functional disorders represent a distinct and common category of genuine illness repeatedly fails to gain traction in these discussions, despite resolving this unhelpful separation of mind and body.

The framework of predictive coding has been particularly helpful in understanding functional disorders. Perception is an interpretation of the world, an inference determined partly by sensory inputs and partly by predictions based on past experiences. Perception can deviate from sensory information if expectations are strong (as in placebo analgesia) or if sensory inputs are imprecise (eg, mishearing what was said in a noisy room). Events like media reports or a friend's illness can lead us to expect, look out for, and ultimately experience particular symptoms. Once symptoms arise, a cycle of irritation, attentional bias, and sensory distortion can be set in motion. Crucially, within this framework, no clear dividing line between psychogenic and organic factors can be drawn.

Unfortunately, our health systems and even our vocabulary are based on a dualistic model. We struggle to conceptualise our brain as a dynamic organ, constantly remodelling itself to make the internal and external world more predictable. The simplistic narratives of brain injury victims or work-shy hysterics sadly come far easier.

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