Biological Psychiatry: Celebrating 50 Years

What's All the Hysteria About? A Modern Perspective on Functional Neurological Disorders

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In the middle of the flanks of women lies the womb, a female viscous, closely resembling an animal; for it is moved of itself hither and thither in the flanks, also upwards in a direct line to below the cartilage of the thorax, and also obliquely to the right or to the left, either to the liver or the spleen; and it likewise is subject to prolapsus downwards, and, in a word, it is altogether erratic. It delights, also, in fragrant smells, and advances towards them; and it had an aversion to fetid smells and flees from them; and, on the whole the womb is like an animal within an animal.

—Aretaeus of Cappadocia, 2nd century AD, on the etiology and treatments of hysteria

Almost 4000 years ago, the Egyptians attributed unexplained physical symptoms in women to abnormal movements of the uterus. This idea remained fixed in medical practice for millennia, with Hippocrates ultimately coining the term "hysteria" (from the Greek word for uterus) to describe such cases. The term remains in common use today: colloquially, it refers to any sort of madness or inexplicable behavior; clinically, it most commonly refers to unexplained neurologic symptoms. These symptoms—ranging the gamut from seizure-like episodes to paralysis—are both common and vexing for clinicians. But until recently, researchers have made relatively little progress toward understanding what causes these syndromes (spoiler alert: it is not a wandering uterus).

Around the turn of the last century, Charcot and then Freud made the critical first step of localizing the site of the "lesion" to the mind. Freud was particularly influenced by the case of Anna O., a patient of Josef Breuer, who developed paralysis and an array of symptoms while caring for her dying father. Struck by the temporal coincidence and informed by his previous work with Charcot, Freud postulated that Anna O.'s psychological distress and previous trauma were "converted" into her neurologic symptoms (a phenomenon he ultimately described as "hysterical conversion") (1,2).

The more recent diagnostic label of conversion disorder retains the original connotation: that psychological triggers are the causative factor in such conditions. The same can be said for the clinical modifiers psychogenic, psychosomatic, medically unexplained, and nonorganic (3). These terms are often taken to suggest that these syndromes lack any biological cause or, more darkly, that patients may be feigning their symptoms.

Without empirical evidence to suggest otherwise, it is easy to see how such beliefs could be maintained. For much of the 20th century, investigation using the tools available (initially electroencephalography and later structural imaging) consistently demonstrated normal results in patients with conversion symptoms. These findings seemed to confirm the doctrine that no "biological" explanation existed.

Only recently, with the emergence of functional imaging, has it become possible to explore this question with greater rigor. In a pioneering study, Spence *et al.* (4) used positron emission tomography to test one of the most critical questions about conversion disorder: are these patients feigning their symptoms? They compared three individuals diagnosed with "hysterical" arm weakness to two groups of controls—one group was instructed to mimic the patients' deficit, and the other group was instructed to move normally. If symptoms were feigned, similar patterns of brain activation would be expected between the patients and the group that was instructed to mimic weakness. Instead, distinctive activation was observed between groups (most notably in prefrontal brain areas involved in volition). A follow-up study by Stone *et al.* (5) showed distinct patterns of functional activation in cortical and subcortical motor pathways between patients with conversion weakness and actors who were simulating the same deficit. Taken together, these findings suggest that patients with conversion weakness are not simply faking their symptoms.

Yet these findings may still leave us with a sense of confusion or unease. Patients' movements are using "voluntary" motor pathways—how is it that their perceived sense of control can become uncoupled from their actions? Or, at a more basic level: what is it that ordinarily allows us to experience agency?

Under normal circumstances, each of our actions is accompanied by a sensory prediction of the expected outcome. For example, when we climb stairs or pick up a cup of coffee, we make sensory predictions of what will occur. When sensory inputs confirm our expectations, we experience a sense of control. Sitting at the junction between visual, auditory, and somatosensory inputs, the right temporoparietal junction (TPJ) plays a crucial role in integrating these data and enabling a sense of agency.

It should come as no surprise, then, that lesions to the right TPJ and adjacent right parietal cortex contribute to syndromes that are characterized by a lack of perceived agency. Extreme examples include alien hand syndrome, in which patients experience a limb as moving with a "mind of its own," and hemispatial neglect, in which patients may fail to attend to one side of their body.

Researchers have also studied a range of common positive conversion motor symptoms, including tremor and gait disorders. One fascinating study by Voon *et al.* (6) used functional magnetic resonance imaging in a group of individuals with a history of conversion tremors. When they compared activation

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from conversion tremors to a voluntary reproduction of the same movements, they found decreased activation of the right TPJ and decreased functional connectivity between the right TPJ, sensorimotor cortex, and limbic regions. These data suggest that conversion symptoms may result from a failure to integrate expectation with sensorimotor input, creating the sense that, like an alien hand, the movement is not under one's control.

These findings also allude to a core aspect of how "hysteria" has historically been described. One of the most striking observations—seminal to the development of the theory proposed by Freud and Charcot—was the connection they theorized between negative affect (which was possibly "repressed") and neurologic symptomatology. In a separate study, Voon *et al.* (7) explored the connection between limbic activity and motor pathways with functional magnetic resonance imaging. Potentially consistent with this theoretical framework, they found that patients with conversion disorder showed greater functional connectivity between the right amygdala and the right supplementary motor area compared with control subjects. These data suggest that high affective arousal could, in fact, influence the initiation of movement, at least in some individuals. Therefore, while these patients might not have conscious awareness of the cause of their symptoms, this might offer a potentially unconscious explanation for how and why these patients experience real disturbances in their motor control system.

Where does all of this leave us? Today, we understand that "hysterical" symptoms are quite common, in one study representing 18% of neurology clinic patients (8). Originally considered a "female" condition, it is still diagnosed in women two to three times as frequently as in men (8). While the underlying cause of these symptoms is not yet fully understood, recent neuroscientific research demonstrates several key findings: 1) brain activation patterns indicate that these patients are not faking their symptoms; 2) decreased activation of the right TPJ may reflect a deficit in the pathway responsible for individuals' having a sense of agency over their motor function; and 3) heightened limbic activity, particularly in the amygdala, and heightened connectivity between limbic structures and motor circuitry may represent a mechanism through which strong emotions influence motor control.

As our neurobiological understanding of "conversion" symptoms has grown, our terminology has also evolved. As psychiatrists, we know that words matter. The labels that we choose are significant both in how they influence the clinician's thought process and in how patients understand their illnesses. Recently, the term "functional neurological symptom disorder" has emerged as the preferred diagnostic label. This name is meant to capture the idea that the relevant pathways are structurally intact but functioning abnormally—which is to say, there is a clear difference in brain function in these patients. Of note, a psychological cause may or may not exist and is not required for DSM-5 diagnosis.

Importantly, with our budding understanding of the neurobiology of these symptoms, our approach to treatment has also changed. It is now clear that the first step in treatment is delivery of the diagnosis (9,10), which includes naming the diagnosis (i.e., functional neurological symptom disorder). It is also important to emphasize that the symptoms are real (not feigned) and that the clinician believes the patient. While psychological factors should be explored and addressed, they are not universally present. And, regardless, a modern formulation must integrate the known neurobiology. This approach can help enhance our compassion for a patient group that has historically been marginalized.

At the time that Charcot and Freud were writing, "general paresis of the insane" remained an untreatable form of "madness." It was later discovered to be neurosyphilis and became a treatable medical syndrome—after which the disease and the diagnosis disappeared from clinical practice. As science continues to advance, we may similarly expect to develop increasing understanding of the biological basis of functional neurological disorders, and can hope that, once and for all, "hysteria" will be dismissed from our lexicon.

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