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A Fragile Balance: Dendritic Spines, Learning, and Memory

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Liam's mom knew that her son learned differently than other kids. As a kindergartener, Liam didn't know the alphabet, and he would not learn it until high school. But his mom figured out that she could teach her son words by showing them to him. She began with his name, which she wrote out on an index card and held up for him to see. She said, "Liam," and he said it back. They did this every day for a week until he understood. Then they went on to the next word: *Mom*.

Although Liam could not make sense of individual letters, he was able to learn the shapes of words. Liam's ways of learning, thinking, and feeling were not things that his mom could fully explain. But, over time, she came to intimately understand how these differences influenced her son's life and how she and Liam could work together to accommodate them.

In 1990, just a few months shy of his second birthday, Liam was diagnosed with fragile X syndrome. At the time, patients with fragile X syndrome were identified by a constellation of symptoms and signs, including autism, intellectual disability, anxiety, aggression, seizures, and elongated facial features (1-3). The name *fragile X* came from the appearance of the X chromosome on karyotype: the long arm looked as if a piece had been broken off (1). But little else was known about the underlying pathophysiology of the disease.

One year later, researchers began to gain traction. They found that fragile X syndrome was associated with an abnormally large number of CGG repeats on the X chromosome (1,2). This trinucleotide expansion was shown to silence the expression of a specific gene and its corresponding protein, both of which were named for the illness: fragile X mental retardation 1 (*FMR1*) and the fragile X mental retardation protein (FMRP) (2).

Over the past quarter century, research on fragile X has evolved significantly and has begun to address a fundamental question: how does dysregulation of one gene lead to such broad dysfunction in learning, memory, and cognition? The story that has emerged highlights an essential aspect of neurophysiology that may be relatively underappreciated in clinical settings: namely, the importance of dendritic spines and the role they play in neural plasticity (4).

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The existence of the dendritic spine first came to light thanks to 19th-century neuroscientist Santiago Ramón y Cajal, who observed that certain dendrites were studded with protrusions that resembled “thorns or short spines” (4). We now know that spines only exist on certain types of neurons (including pyramidal neurons in the cortex and Purkinje cells in the cerebellum) (5). There can be over 10,000 spines on a single neuron, each representing a point of synaptic contact at which the cell receives input from another neuron (1,5).

Early in brain development, dendrites are initially spine free. Spines begin to grow when the dendrite plasma membrane starts forming tentacle-like projections called filopodia (4). These protrusions create synapses with nearby axons and eventually mature into spines. Ultimately, about half of these synapses will be pruned during childhood and adolescence (4).

The plasma membrane of dendritic spines is equipped with a flotilla of proteins, including nicotinic acetylcholine receptors, voltage-gated ion channels, scaffolding proteins, and several types of glutamate receptors, including the ionotropic *N*-methyl-D-aspartate and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors, as well as metabotropic glutamate receptors (including metabotropic glutamate receptor 5) (5,6). Many of these proteins are grouped together in the so-called postsynaptic density (6).

Once a spine starts receiving synaptic input, the activation of glutamate receptors induces a panoply of events. Second messenger cascades are triggered, including the mechanistic target of rapamycin pathway, whose activity increases protein synthesis (2,4). Additionally, activation of glutamate receptors enables the influx of calcium, which initiates other cascades that are important for neuronal plasticity (5). Calcium influx also upregulates actin polymerization, allowing the spine to change shape (6).

In the adult brain, spines continue to be protean things; they grow, change, die, and are born in response to the events and environments they encounter. Importantly, dendritic spines are where some of the key processes that facilitate learning and memory take place (4,5). These processes include long-term potentiation and long-term depression, which are means by which axons strengthen or weaken connections to their target neurons by using particular patterns and intensities of stimulation. Long-term potentiation can cause spines to expand within seconds, whereas long-term depression can cause spines to shrink (Figure 1A) (5,6). The more that spines are stimulated, the bigger, more stable, and longer lived they become (in contrast with smaller, immature spines, which are more transient) (6). These large, so-called mushroom or stubby spines are thought to be one of the physical correlates of memory (4).

The interplay between experience and memory as mediated by dendritic spines was elegantly explored by Yang *et al.* (7) in 2014. Yang *et al.* taught mice to run on a rotating rod and, in each mouse, they imaged motor neurons (which reside in cortical layer V). They saw that after the mice ran forward on the rod, their layer V neurons formed new spines on some dendritic branches, but not others (these so-called learning-induced spines are correlated with long-term motor skill retention). If the mice ran forward on the rod again, they tended

to form more spines on the same branches. If they ran backward, they formed new spines, but on different branches.

Some of the mice were kept awake for several hours after they ran, while others were allowed to sleep. In the brains of the mice who slept, the same neurons that had fired while the mice were running started firing again during sleep. Ultimately, the mice who slept formed spines that were longer lasting and more numerous than those formed by their sleep-deprived peers. As other studies have suggested, a slew of external factors in addition to sleep (including stress, depression, nicotine, serotonin, and estrogen) seem to be capable of affecting the number and/or shape of dendritic spines (6,8).

We began our discussion with Liam, who is now 29 years of age and remains part of a deeply loving family. However, he continues to have anxiety, agitation, and—as a core deficit—difficulty with learning. When Liam was first diagnosed with fragile X syndrome, relatively little was known about the disease. Now, after 25 years of research, we understand that in many ways, fragile X syndrome may be conceptualized as a disease of dendritic spines.

In patients with fragile X syndrome, spines are elongated, tortuous, and densely packed, and they are thought to undergo rapid turnover (4). These abnormalities may be linked to the absence of FMRP, which is thought to regulate messenger RNA translation (2,4). Without FMRP, it is thought that protein production (which is intimately involved with synaptic plasticity) becomes dysregulated. In the setting of this instability, patients are thought to have elevated long-term depression (seen in fragile X syndrome mouse models) and impaired synaptic plasticity (4). Although we have focused here on neuronal dysfunction in fragile X syndrome, a deficiency of FMRP in astrocytes also likely contributes to the abnormal spine structure and impaired learning seen in fragile X syndrome, as Hodges et al. (9) illustrate in this issue of *Biological Psychiatry*.

A multitude of genes that have been implicated in autism spectrum disorder, schizophrenia, and intellectual disability are thought to encode proteins that affect spines and synapses (4). Spines have been noted to be grossly abnormal in a myriad of conditions. For instance, there are thought to be too many spines in some forms of autism spectrum disorder and too few spines in depression and Alzheimer's disease (Figure 1B) (8). Decreased spine density has also been observed in schizophrenia. While this was initially thought to reflect excessive pruning of existing synapses, recent work suggests that patients with schizophrenia may actually have too few of the small, immature spines that are involved in formation of new synapses (10).

Intriguingly, some psychoactive medications—including selective serotonin reuptake inhibitors and ketamine—have been shown to restore spine density in rodent models of depression (8). Moreover, and of relevance to Liam's story, some of the most exciting research in modern neuroscience has involved working to reverse the known lesions in fragile X syndrome. For instance, metabotropic glutamate receptor 5 inhibitors (postulated to decrease excess protein synthesis) have been shown to improve learning and memory in mouse models of fragile X syndrome (2). While these agents have not demonstrated clear

benefit in clinical trials, new pharma-cotherapies are in the works, including a p21-activated kinase inhibitor that rescues autistic symptoms and normalizes spine density in fragile X mental retardation 1 knockout mice (3).

Between an X chromosome and a boy who learns words by their shapes, there remains a complex puzzle. Although piecing this together is certainly a daunting task, new research is making significant inroads into our understanding of fragile X syndrome and the role of dendritic spines in learning and memory. Fortunately, researchers seem to be identifying molecular targets that may prove to be helpful in developing more precise pharmacologic and behavioral therapies—not only for patients with fragile X syndrome, but also potentially for the broader community of patients affected by intellectual disability and autism.

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Figure 1.

Dendritic spines can experience spontaneous fluctuations in shape. Their size can also change in response to synaptic stimulation in the form of long-term depression or long-term potentiation. This is called activity-dependent plasticity. (A) Repeated long-term potentiation causes spines to become larger and heartier. This process is thought to be important in the creation of memories. (B) Dendritic spines can appear abnormal in different neuropsychiatric disease states. Postmortem studies have shown a decreased number of spines in patients with depression; elongated, tortuous spines in patients with fragile X syndrome; and fewer spines, some with large heads, in patients with Down syndrome. Adapted from Kasai et al. (5) and Phillips and Pozzo-Miller (4).