

TERRENCE SEJNOWSKI

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How do we remember the past?

There are many answers to this question, depending on whether you are an artist, a historian, or a scientist. As a scientist, I want to know the mechanisms responsible for storing memories and where in the brain memories are stored. Although neuroscientists have made tremendous progress in uncovering neural mechanisms for learning, I believe (but cannot yet prove) that we are all looking in the wrong place for where long-term memories are stored.

I have been puzzled by my ability to remember my childhood even though most of the molecules in my body today are not the same ones I had as a child – in particular, the molecules that make up my brain are constantly being replaced with newly minted molecules. Despite this molecular turnover, I have detailed memories of places where I lived

fifty years ago – memories that I never rehearsed but which are easily verified.

If memories are stored as changes to molecules inside brain cells – molecules that are constantly being replaced – how can a memory remain stable over fifty years? My hunch is that the substrate of old memories is located not inside the cells but outside, in the extracellular space. That space is not empty but filled with a matrix of tough material that connects cells and helps them maintain their shape. Like scar tissue, the matrix is difficult to dissolve and is replaced very slowly, if at all. (This explains why scars on your body haven't changed much after decades of sloughing off skin cells.)

My intuition is based on a set of classic experiments on the junction between motor neurons and muscle cells. When the neuromuscular junction is activated, the muscle contracts. If the nerve that activates a muscle is crushed, the nerve fiber grows back to the junction, forming a specialized nerve terminal ending. This occurs even if the muscle cell is also killed. The 'memory' of the contact in this case is preserved by the extracellular matrix at the neuromuscular junction, called the basal lamina. The extracellular matrix at synapses in the brain may have a similar function and could well maintain overall connectivity despite the comings and goings of molecules inside neurons.

How could we prove that the extracellular matrix is responsible for long-term memories? The theory predicts that if the extracellular matrix is disrupted, memories will be lost. This experiment can be done with enzymes that selectively degrade components of the extracellular matrix or by knocking out one or more key molecules using molecular genetic techniques. If I'm right, then all of your memories – what makes you a unique

individual – are contained in the brain's exoskeleton. The intracellular machinery holds memories temporarily and decides what to permanently store in the extracellular matrix, perhaps while you are sleeping. It might be possible someday to stain this memory exoskeleton and see what our memories look like.