In 1972 the distinguished neurologist Fred Plum famously labeled efforts to reveal structural changes in the brain in schizophrenia the “graveyard of neuropathologists.” This conclusion came on the heels of research dating back to the late 19th century, including failed efforts by Alois Alzheimer to identify areas of the brain in schizophrenia that suffered cell loss (he had much more success in finding the pathology associated the eponymous form of dementia). Despite a variety of early investigations that purported to find structural brain changes in the disorder, these findings could not be replicated. By the middle of the 20th century attempts to identify brain lesions in psychosis languished, and a generation later Plum issued his grim assessment of the state of schizophrenia research.

Over the past fifty years, however, the story has been far more positive. The introduction of quantitative neuroanatomical methods applied to postmortem material and the development of in vivo imaging techniques that allow us to peer into the living human brain yielded macroscopic and microscopic data that clearly demonstrate that schizophrenia, in which people experience delusions, hallucinations, and trouble thinking and managing their emotions, is a brain disease.

Because schizophrenia is usually first diagnosed in adolescents or young adults after an early-stage period of unusual behavior (withdrawing from friends, or acting out), and because there are a number of early developmental events that are associated with an increased risk for developing the illness, schizophrenia is considered a neurodevelopmental disorder. This type of disorder is characterized by some life event triggering a cascade of subsequent steps that over time culminate in overt symptoms. Because neurodevelopmental disorders result from an event that may occur long before symptoms emerge, there is hope that new treatments could derail the progression to overt psychosis. Current antipsychotic drugs treat only the positive symptoms such as delusions and hallucinations, and those relatively poorly, so there is a strong need for new approaches to managing schizophrenia, including efforts to prevent as well as treat symptoms. Neurons communicate at the synapse, a specialized structure where the tip of the axon from one neuron (pre-synaptic) abuts a dendrite, the receptive structure of another neuron (the post-synaptic neuron). The communication between these two neurons is mediated by neurotransmitters. These molecules are released from the tip of the presynaptic neuron and spread across a narrow stream of extracellular fluid to activate receptors on the postsynaptic neuron. Several studies of brain development have found that the numbers of synapses on neurons increase early in life to finally peak in late childhood and early adolescence, after which the number declines (“pruning” of synapses) until the synaptic density stabilizes at its mature state. The age at which neurons achieve their adult synaptic density differs across various brain regions; the prefrontal cortex (PFC) is the last to stabilize, during the third decade of life. This is the age at which a person at risk for schizophrenia first manifests psychosis. Moreover, the PFC is critically involved in attention, working memory, and other cognitive processes that are disturbed in schizophrenia.

Why is the temporal pattern of synapse changes during development important for schizophrenia? The striking correspondence of the timing in changes in synaptic density in the PFC and the appearance of symptoms led the psychiatrist and noted sleep researcher Irwin Feinberg to hypothesize that schizophrenia results from a defect in the synaptic elimination programmed to occur during adolescence.
This hypothesis, put forth in 1982, was attractive because it accounted for the time course of symptom appearance in schizophrenia and suggested that a derangement in synaptic communication in the PFC was underlying the symptoms. While Feinberg’s hypothesis has been influential, it was based on data from healthy people; there were scant direct data on synaptic counts in the PFC from postmortem studies in schizophrenia.

Over the past 20 years a number of postmortem studies have independently shown that the density of dendritic spines, the structure on which excitatory neurons synapse, is decreased on PFC neurons in brain tissue from people, who had been diagnosed with schizophrenia before death. The number of dendritic spines on neurons of people with schizophrenia were reduced by one-third or more. Although these postmortem studies of dendritic spines were performed on tissue samples from people who had schizophrenia for an extended period of time, they are consistent with (but do not prove) Feinberg’s hypothesis of a neurodevelopmental onset of the illness, with an event occurring during adolescence manifesting itself years later. Considerable effort has been devoted to studying the loss of dendritic spines on PFC neurons, with a focus on identifying the characteristics of cells that undergo spine loss and the molecular underpinnings of the phenomenon. Much less work has focused on determining where did the “lost” spines go?

The answer to this question brings us back to how brains develop. Until now we have discussed neurons, which synapse with one another to form circuits that connect different areas of the brain. Other cells in the brain, collectively called glia, have historically been thought of as secondary cells that provide structural support, encase axons in an insulating material so that communication of signals from one part of the neuron to its distal end is faster, and maintain brain appropriate levels of brain molecules. There are three major classes of glial cells: microglia, astrocytes, and oligodendrocytes. Astrocytes provide metabolic energy to sustain neurons and regulate the extracellular concentration of neuroactive substances such as glycine, glutamate and adenosine. Oligodendrocytes elaborate myelin, the lipid sheath incasing axons to speed electrical impulse down the axon.

Microglia are moderately-sized cells with spider-like arms that are the resident immune cells of the brain. The arms of microglia radiate outward from the cell body and survey the brain for signs of foreign invaders or injury. If detected, these invaders trigger an immune response that culminates in microglia engulfing and digesting the foreign or damaged material. Only recently have we found that microglia are also critical for the pruning of healthy synapses, including both dendritic spines and axon terminals, during development. When neurons in the PFC reach their peak density of dendritic spines in late childhood, microglia move in to remove excess spines. (Although microglia play a major role in this process, the astrocyte, another type of glial cell, also contributes to pruning.) The key role of microglia in sculpting the final form of neurons suggests that if the actions of microglia are abnormally enhanced during adolescence the result would be an abnormally low number of dendritic spines and synapses on PFC neurons, as seen in schizophrenia.

New genetic data also point to microglia as being involved in schizophrenia. The disorder runs in families: Studies of identical twins in the 1960s found that if one twin has schizophrenia, the risk of the other having or developing the illness approaches 50 percent. However, extensive studies using increasingly sophisticated genetic analyses have found that there are dozens of genes that are associated with schizophrenia, each contributing very little to overall risk, and many showing up only in a single family. One signal, though, has been repeatedly identified in genetic studies of schizophrenia. It indicates that there is an association between schizophrenia and the region of chromosome 6 that houses genes of the major histocompatibility complex (MHC).

Major histocompatibility genes encode proteins expressed on the surface of cells that mark the cell constituents as being self (and hence not attacked as foreign) or non-self. Steve McCarroll and colleagues recently performed a very detailed examination of the region of chromosome 6 that includes the MHC genes in more than 60,000 people with and without schizophrenia. The researchers were able to narrow down the region of chromosome 6 to a much smaller area that included a gene for a constituent of the immune system named complement C4. Geneticists graphically depict how strongly associated a given gene is with a particular population (e.g., persons with an illness) using a Manhattan plot. This visual representation closely resembles the Manhattan skyline, with skyscrapers of varying heights, the tallest...
representing the most significant difference. The C4 peak on the Manhattan plot looks like a misplaced Empire State Building arising from the plains of Nebraska.

Complement factors such as C4 are part of the immune system that enhance (complement) the ability of scavenger cells (which in the brain include microglia) to respond to invasive cells or proteins. Complement C4 is closely associated with another complement factor, termed C3, which is deposited on synapses to mark them as destined for pruning; C4 directs C3 to move from glia to synapses between neurons. Thus, microglia eliminate synapses by identifying which synapses are to be eliminated and then by removing them from neurons.

There is now an intense effort to understand the mechanisms that promote microglial pruning of synapses, which would illuminate paths to the development of new treatments for schizophrenia. As noted earlier, the loss of dendritic spines on PFC neurons is partial, with many spines being spared. We don’t know what accounts for some spines being removed and others left intact.

As cells of various types die, both because of aging or damage, there are several different kinds of signals that inform scavenging cells which dying cells should be engulfed and digested. The same process occurs on parts of neurons destined for elimination. There is an “eat-me” signal that informs the microglial cell to remove a particular synaptic spine (for example, one marked by C3). There are separate “find-me” signals that draw the microglial cell close to the marked spine. There are even “don’t-finder-me” signals, a sort of repellant molecule that allows the spine to evade pruning. These different processes of finding and then engulfing a spine are targets for novel drug development. For example, if we could identify a drug that amplifies the “don’t-find-me” signal during the early phase of pruning of excess spines, prior to the onset of schizophrenia (during the prodromal period leading up to the first psychotic episode), we might prevent the excess pruning of dendritic spines on PFC neurons and thereby prevent subsequent pathology. Similarly, an antagonist of the “eat-me” signal would prevent pruning of excess spines. This may be a double-edged sword, however, with the prevention of spine pruning leading to too many spines on a neuron, which is in turn harmful and has been associated with autism spectrum disorder.

It is now quite clear that schizophrenia is a brain disease, with structural changes in the architecture of individual neurons and in turn different brain regions that when dysfunctional contribute to the emergence of various symptoms. The recent discovery of key roles of non-neuronal cells such as microglia in the development of schizophrenia would have been inconceivable to researchers of the last century. While adding an unanticipated level of complexity to understanding the brain mechanisms that are deranged in schizophrenia, our new understanding opens the door to novel therapeutics for an illness in which responses to current treatments are woefully incomplete.

Further Reading
- Probing Synaptic Pruning – Dana news story (2014)
- Dendritic spine – Wikipedia
- Synapse Formation, Survival, and Elimination – Andrew Bean, textbook chapter on Neuroscience Online
- Why ‘Synaptic Pruning’ is Everywhere—And What it Means to You – Theresa Fisher, Van Winkle’s blog
- Complement system – Wikipedia

References