How and why should we build a wiring diagram of the brain?

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Neurons are specialized to communicate information. However, not all neurons are wired together, meaning that some are capable of communicating with one another, while others are not. The pattern of connections made by neurons—the brain's 'wiring diagram'—determines how behavior, cognition, and emotion arise. Understanding this diagram is crucial both for our basic knowledge of the mechanisms of brain function, and for investigating and treating psychiatric and neurological disorders.

First, I will discuss how the brain's wiring diagram can help us to use nonhuman animal models of brain disorders more effectively. Rodents (both rats and mice) are essential nonhuman animal models in the field of neuroscience. They offer unprecedented access to genetic, molecular, and pharmacological tools unusable in both humans and nonhuman primates. Unfortunately, rodent brains are certainly not human brains: they are not only much smaller, but may simply lack many of the same brain regions present in human brains. Determining which regions of the rodent brain are similar to those in the human brain is simultaneously very challenging and very urgent. I use connectivity as a defining metric of brain regional similarity across species. I have performed these studies in the prefrontal and posteromedial cortices. I was able to use connectivity with conserved brain structures to determine which portions of the brain are similar and dissimilar to different portions of the primate cortex.

Second, I will look carefully at how we can untangle the wiring diagram of the *human* brain. Unfortunately, we are fundamentally limited in the tools available to study neuronal connectivity in the human brain. One of these tools, diffusion magnetic resonance imaging (dMRI) takes advantage of the differential diffusion of water molecules along axons traversing in different directions to try to estimate connectivity between populations of neurons. Unfortunately, dMRI does not accurately match the connections that anatomical studies have demonstrated (in nonhuman animal work). dMRI is susceptible to both false positives (identifying connections that should not exist) and false negatives (failing to pick up on true connections). I have developed a pipeline to combine non-invasive, dMRI-derived measures of brain connectivity with anatomical tract-tracing in nonhuamn primates, with the goal of learning about human brain connectivity. Such cross-species comparisons are a critical step in delineating the full range of human brain connections.