CLINICAL IMPLICATIONS OF BASIC RESEARCH

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On Synaptic Circuits, Memory, and Kumquats

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The human brain is a network of nearly 100 billion neurons forming as many as a quadrillion synapses. Exactly how this massively distributed information processor produces and represents mental content remains one of the most formidable mysteries in science. A growing number of researchers consider a comprehensive, detailed map of brain synaptic connections (the "connectome") to be useful, even necessary, for cracking the neural code. After all, how can we hope to understand the functional organization of such complex machinery without a reliable circuit blueprint? Hence, there has been a recent surge of "connectomics," accompanied by claims that many neurologic and psychiatric conditions, including Alzheimer's disease, schizophrenia, depression, and autism spectrum disorders, are connectopathies.

Although most of the progress in deciphering the human connectome has made use of noninvasive whole-brain imaging, those approaches capture only macroscopic regional connectivity without providing information on the axonal (output) and dendritic (input) wiring of individual neurons. In contrast, basic research in animal models relies on microscopy. Optical microscopy can be used to scan fields of view that are large enough to encompass the substantial area of the brain that the axon of a single projection neuron typically traverses, but (with the exception of super-resolution microscopy) it lacks the resolving power to definitively identify synapses. Electron microscopy, conversely, can detect every last neurotransmitter vesicle — but, alas, in only a minuscule region of interest that is inadequate for capturing the extent of just one long-range axon. In a recently reported study, Kasthuri and colleagues[1] use the full power of electron microscopy in a complete volumetric reconstruction of the local surroundings of several dendritic trees in the mouse neocortex.

This work is noteworthy for three reasons. First, it explicitly shows the massive scale of dense synaptic connectomics: although the reconstruction of this region represents considerable progress in the automation of technologies for the required scale-up of both raw-data acquisition (histology and imaging) and computational analysis (tracing and annotation), it amounts to only a tiny proportion of a single mouse cortex. Second, the authors publicly shared the entire collection of original microscopic images and the analyzed subset of processed data online, providing a valuable resource for additional reconstruction and data mining. Third, the quantification of the extracted circuit and its spatial embedding proved the exquisite selectivity of network connectivity: the physical proximity of axons and dendrites was not sufficient for the prediction of synapse formation (Fig. 1A). In other words, the probability of finding a synapse between two neurons is not proportional to the number of spatial overlaps between their respective axons and dendrites.

What does this finding reveal about the relationship between neural structure and cognitive function? Because network connectivity constitutes the structural substrate for information transmission, the synaptic matrix determines the set of all possible activity patterns that a given brain can instantiate — that is, it determines the content of an individual's memory. According to this logic, synaptic formation or elimination would then correspond to learning or forgetting.[2] Thus, axonal–dendritic overlaps constitute not only required conditions but also potential opportunities for the formation of new synapses. In Hebb's "fire together, wire together" model of experience-dependent plasticity, two neurons form a synapse if their respective axons and dendrites are both mutually juxtaposing and consistently coactivated.

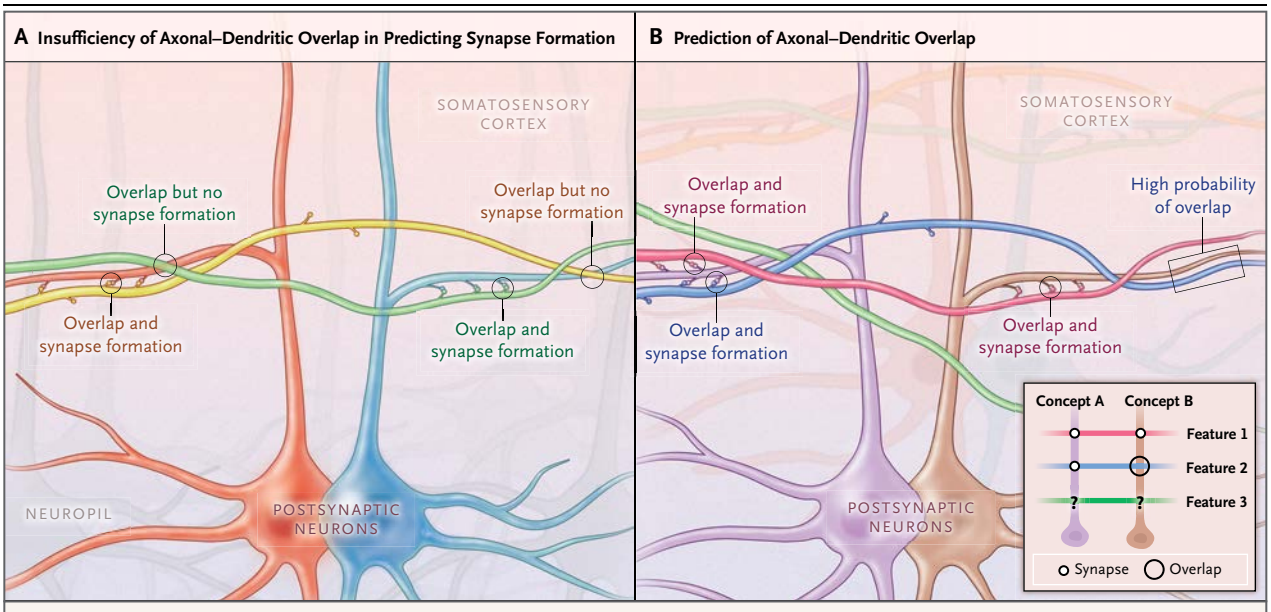

Figure 1. Fundamental Rules of Neural Connectivity: Axonal–Dendritic Overlaps and Synaptic Selectivity.

The saturated reconstruction of a small volume of mouse somatosensory cortex with the use of electron microscopy, reported by Kasthuri et al.,[1] shows that spatial overlap of axonal and dendritic branches is strictly necessary — but not in itself sufficient — to predict synapse formation. In Panel A, two neurons and their dendrites are schematically highlighted (red and blue). Two axons are also shown (green and yellow) with their respective synaptic contacts, in an illustration of the selectivity of the circuit: although both axons are physically overlapping with both dendrites, the green axon mainly forms synapses with the blue dendrite, whereas the yellow axon mainly forms synapses with the red dendrite. The light gray axons and the neurons and dendrites in the background illustrate that the reconstructed volume is dense with neuropil. Panel B shows the two-way relationship between axonal–dendritic overlap and synaptic connectivity, which crucially constrains network circuitry. Although synapses must necessarily represent a subset of axonal–dendritic overlaps, the synaptic connectome also provides information on the probability that two neurons might have an axonal–dendritic overlap. For instance, the dark blue axon is likely to overlap with the brown dendrite, because it synapses with another dendrite (purple) that is also contacted by an axon (pink), and this axon also contacts the brown dendrite. The green axon does not connect with these two dendrites and is thus in a less suitable position for the formation of spatial overlaps. The inset provides a schematic summary of this relationship (with synapses denoted by solid circles and axonal–dendritic overlaps denoted by open circles), under the simplifying assumption that postsynaptic neurons encode concepts and incoming axons encode related features. Concepts A and B are similar (because they share Feature 1), and therefore Concept B has a greater opportunity to become associated with other features of Concept A (such as Feature 2) than it does with other features (such as Feature 3).

Even without synapses, however, the set of axonal–dendritic overlaps in the cortex might have its own fundamental cognitive correlate. Wiring parsimony suggests that neuronal branches do not meander aimlessly: an axon passes near a dendrite only to contact another close dendrite. Similarly, two dendrites are likely to be neighbors if they receive many common inputs. Stated differently, adjacent neurons tend to encode similar content by virtue of optimal placement, and this is consistent with the topographic organization of the cortex (Fig. 1B). Therefore, axonal–dendritic overlap also implies that there is conceptual compatibility of the corresponding mental content.[3] For example, a hypothetical axon encoding sour–sweet taste, thanks to the multiple synapses it makes in the cortical region that encodes the perception of the tastes of fruit, is likely to overlap with a hypothetical dendrite, located in the same space, that encodes the taste of kumquats. The prerequisite of physical proximity for synaptic formation could then explain why learning requires relevant background knowledge.[4] Recent computational studies have shown that this constraint also reduces the incidence of incorrectly learning spurious associations of randomly co-occurring events relative to real causal relations.[5] For instance, when eating a kumquat for the first time while listening to a song, a person is more easily able to associate the fruit with its taste than with the melody.

Because synaptic connectivity is also dependent on neuronal identity rather than only on location, Kasthuri and colleagues conclude that

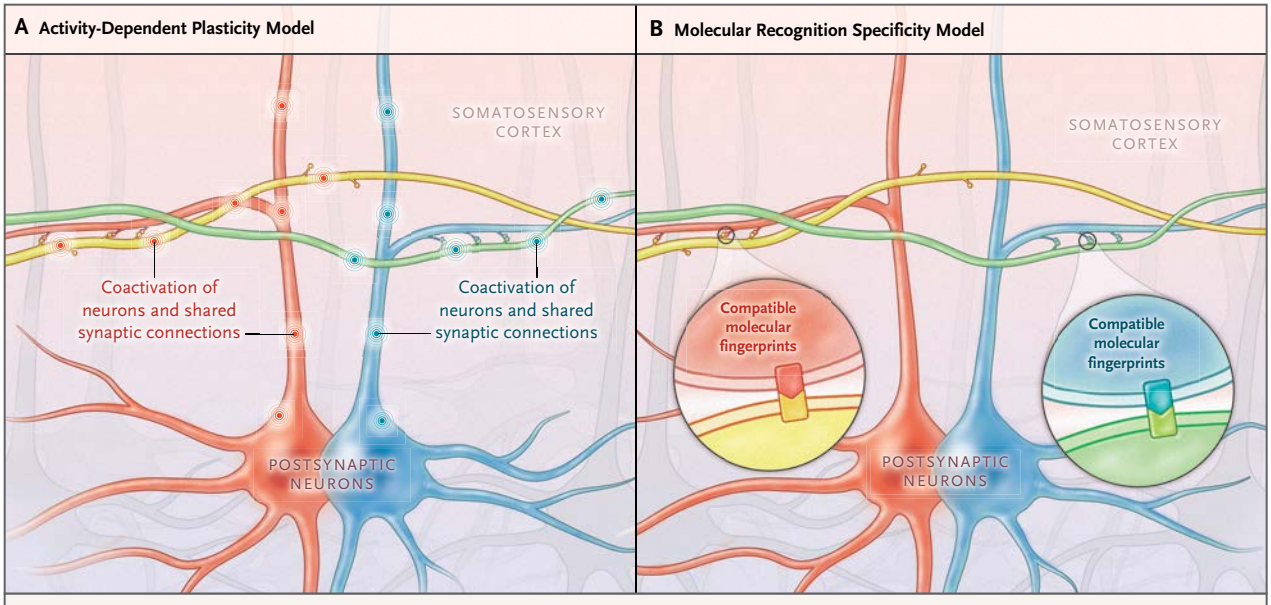

Figure 2. Models of Determinants of Synaptic Selectivity.

Activity-dependent plasticity is one means of explaining synaptic selectivity (Panel A). An animal can learn a number of associations (corresponding to all axonal–dendritic overlaps in its brain) through exposure to the appropriate environmental stimuli. Of these, only those few stimuli that are in fact experienced ("fire together") are reflected in actual synapses ("wire together"). In this example, the synaptic connections are consistent with past coactivation of the yellow axon with the red dendrite (red discharges), but not with the blue dendrite, and vice versa for the green axon (blue discharges). Alternatively, synaptic selectivity could rely on molecular recognition specificity (Panel B). In this model, individual neurons would express a unique combination of genes and proteins that allows them to select their synaptic partners on the basis of compatible molecular fingerprints.

optical microscopy is insufficient for circuit mapping and that electron microscopy is necessary. The two techniques could instead be viewed as addressing complementary questions: by tracking all synapses, electron microscopy might measure stored knowledge memorized from past experience. A map of axonal and dendritic branching distributions obtained by means of optical microscopy, in contrast, could reveal potential future memories to be learned, given the appropriate experience. The observed selectivity of cortical synapses is consistent with this model of activity-dependent structural plasticity, in which axonal–dendritic overlaps do not constitute simple probabilities but rather capabilities of forming synapses (Fig. 2A). A non–mutually exclusive alternative model could also explain synaptic selection as being a result of neuron-specific molecular recognition (Fig. 2B). The distinction between these two mechanisms is clinically relevant, given the promising prospects of pharmacologic intervention to treat memory malfunction.

Paradoxically, although electron microscopy was instrumental in providing evidence that synaptic formation is not just a random consequence of axonal–dendritic overlaps, optical microscopy currently appears better equipped both to record neuronal activity in vivo and to characterize intracellular biochemical content. Thus, fully understanding the links between brain circuitry and computational function will probably require continuous parallel advancement of the two approaches.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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