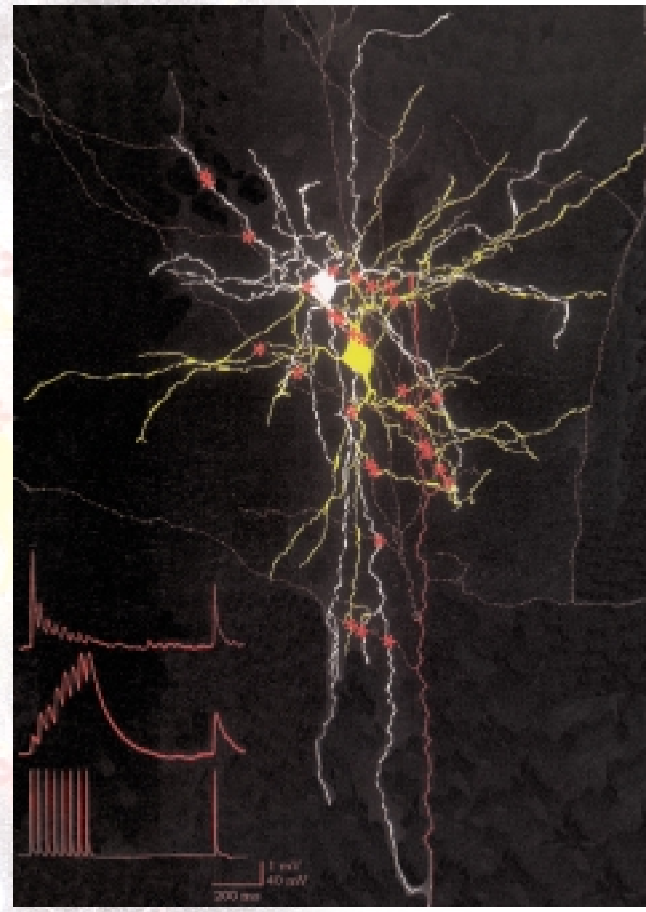
Research Note:

Brain Connections Unexpectedly Diverse

Every nerve cell (neuron) receives numerous incoming electrical signals via a bushy "forest" of electrically sensitive filaments called dendrites. It processes this information and then sends an integrated outgoing signal along its long, straight axon to the dendrites of the next neurons in its signaling pathway. This last step involves the transmission of neurotransmitter chemicals across special gap-junctions (synapses) that both separate and connect the axonal ends of one neuron to the dendrites of the next neurons in line. This simple model has been radically revised by recent work by Weizmann Institute researchers Profs. Misha Tsodyks, Henry Markram and their colleagues.



In a groundbreaking series of theoretical and neurophysiological studies, reported in *J. Physiology* (1999), *Science* (2000), *J. Neuroscience* (2000) and other prestigious international journals, they find that synapses do not simply transmit each incoming electrical signal (action potential, AP) equally. Rather they react differently to specific patterns of AP's and their transmissions reflect prior AP activity. In the researchers' more realistic computer model of a network of neurons linked by activity-dependent synapses, AP activity spontaneously organized itself into highly synchronized bursts, resembling activity-gated reflexes found in nature. Another model, in which the probability of neurotransmitter release at a synapse, depended on whether the transmitting neuron had spiked recently (100 msec. or less) before or after the receiving one, readily matched neurophysiological observations and demonstrated a form of synaptic "learning."

More surprisingly, the researchers' careful multi-neuron study of the pyramidal neurons (PN) and interneurons (IN) of the brain's neocortex, revealed that even synapses using the same neurotransmitter (e.g., GABA) can come in several quite distinct types, and that the same neuron may use more than one type of synapse. Indeed, the *same* axon often makes quite different connections to different cells, in a cell-cell (PN-PN, PN-IN, etc.) specific manner. That is, cortical neurons can and do simultaneously transmit several quite different messages at once! This crucial aspect of the brain's circuitry was missed in previous neurophysiological studies of individual neurons or neuron pairs.

The accompanying computer-processed, photomicrograph-based reconstruction shows a pyramidal neuron (red) and its presumed synapses, with two interneurons (yellow and white). For simplicity, only the axon projections of the transmitting pyramidal neuron and the cell bodies and dendrites of the receiving their neurons are shown. When the red pyramidal neuron is electrically stimulated as shown in the bottom oscilloscope trace, the electrical activity of the white interneuron is facilitated, while that of the "yellow" interneuron in depressed.

In all, Israeli researchers find eight electrophysiologically distinct subclasses of interneurons which use three distinct types of GABA synapses. Combining this with observed anatomical/morphological variations, gives 14 distinct cell types (each anatomical class has only a few types of electrophysiological subclasses). Each subtype of interneuron makes only one specific type of connection (synapse) to a pyramidal neuron, and presumably vice versa. The type of synapse to be formed is apparently "negotiated" by the neurons on each side.

Finally, all GABA (but not glutamate) synapses of the *same* type display similar time-pattern behavior for all the possible neuron combinations using that synapse type. That is, such neurons form "GABA groups" with similar dynamics (since a single IN cell can have several different types of GABA synapes it can belong to more than one group). All PN cells, and some IN cells, in layers II-IV of the brain's neocortex are expected to be in the same GABA group. Such groups represent the most elementary, functionally related groups of neurons known in the neocortex.