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Dendritic spines

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1. Introduction

Around the turn of the century Ramon y Cajal (1891) first discovered the tiny protrusions called "dendritic spines" that stud the surfaces of neurons throughout the brain. He and his contemporary, Tanzi, postulated that changes in spine structure or number would be important factors in synapse formation during development and synapse modification during learning and memory in the mature nervous system. Later, **Gray (1959)** discovered with electron microscopy (EM) that dendritic spines are indeed the key postsynaptic targets of excitatory axons in most brain regions. Results from numerous studies are beginning to show evidence for alterations in dendritic spines during development, with learning and memory, and with long-term potentiation, a physiological model that is widely studied as a candidate cellular mechanism of some forms of learning and memory.

2. Structure and composition of dendritic spines

For detailed descriptions and reconstructions of dendritic spines and their synapses consult our website called "Synapseweb" located at **http://synapses.mcg.edu**. Some of the following figures are directly bookmarked to the website.

2.1. Spine shape

Dendritic spines assume striking differences in size, shape, and subcellular composition both within and across brain regions (**Figure 1**). Most spines are unbranched protrusions that can be classified by their stubby, thin, or mushroom shapes (**Figures 1** and **2**). Branched spines have multiple heads which in some brain regions are all innervated by a single axonal bouton (e.g., hippocampal area CA3; see Chicurel and Harris, 1992); in other brain regions the different heads of a branched spine are innervated by different axons (e.g., hippocampal area CA1; see Harris, Jensen, and Tsao, 1992); and in rare cases some of the heads have no presynaptic partners while other heads are innervated by different axons (e.g., cerebellar Purkinje spiny branchlets; see Harris and Stevens, 1988).

2.2. Synapses

Usually an asymmetric synapse with a thickened postsynaptic density (PSD) occurs on the spine head across from the presynaptic axon which contains round clear vesicles (**Figure 1**). This arrangement is typical for excitatory glutamatergic synapses. Serial EM reconstruction reveals continuous PSD surfaces (i.e., macular) on all of the different spine shapes, while perforated PSDs are specifically associated with larger mushroom-shaped dendritic spines (**Figure 2**). Some spines also have a symmetric, inhibitory synapse located on the spine neck (**Knott et al., 2002**), although the presence of this second synapse is not universal, and in several brain regions, including hippocampus, none of the spines have a second synapse. Numerous proteins have been identified in PSDs including: neuroreceptor glycoproteins, protein kinases, structural and mechanochemical proteins, proteins involved in endocytosis, and proteins involved in the glycolytic pathway (reviewed in **Kennedy, 2000**; **Sheng, 2001**).

There is more than a 100-fold variation in dendritic spine and synaptic dimensions. The differences in spine and synapse morphology and composition likely reflect different synaptic histories due to developmental and use-dependent mechanisms such as learning and memory. Despite the gross differences the PSD has been found to occupy approximately 10% to 15% of the total spine surface area in all brain regions tested so far. This consistency suggests that the non-synaptic membrane must be present in a particular proportion to support synaptic function.

2.3. Organelles

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Smooth endoplasmic reticulum (SER) is an organelle that is likely to be involved in sequestering calcium. Depending on the particular brain regions, few, many, or most of the dendritic spines contain SER (**Fig. 1**). For example, only about 14% of the hippocampal CA1 spines contain SER (**Cooney et al., 2002**), and most of it occurs laminated with dense-staining material into a structure known as the spine apparatus (as in **Fig. 1**) in the large, complex spines. In contrast, nearly 100% of the cerebellar Purkinje spines contain SER in a tubular network (**Harris and Stevens, 1988**; **Martone et al., 1993**). Local protein synthesis occurs in dendritic spines because polyribosomes can be observed in some, but not all spines, reflecting the dynamic nature of protein synthesis (**Fig. 3**; reviewed in **Steward and Schuman, 2001**). Similarly, endosomal compartments

including coated pits and vesicles, large vesicles, tubules, and multivesicular bodies are restricted to a subpopulation of dendritic spines that differs from spines that contain SER (**Cooney et al., 2002**). Mitochondria rarely occur in dendritic spines and are restricted to very large, complex, and highly branched dendritic spines (**Chicurel and Harris, 1992**).

2.4. Cytoskeleton and cytoplasm

A loose network of filaments characterizes the cytoskeleton of dendritic spines. Spine cytoskeleton differs from dendrite cytoskeleton by the absence of microtubules in spines, except for the occasional microtubule in highly complex spines. The spine cytoplasm is comprised of actin and actin-regulating proteins (**Matus, 2000**), which are longitudinally situated in the spine neck and organized into a dense lattice surrounding the SER or spine apparatus in the head. This organization of the actin filaments suggests that they provide the scaffolding for the basic spine structure, as well as mediate changes in spine shape. Other molecules found in the spine cytoplasm that may interact with the actin cytoskeleton, usually in a calcium dependent manner, include: calmodulin, myosin, brain spectrin (fodrin), and MAP-2.

2.5. Presynaptic vesicles

The axons associated with dendritic spines make en passant boutons, which contain numerous round clear vesicles. The membranes of the axon and vesicles contain specific molecules involved in vesicle formation, docking, and release. On the cytoplasmic side of the presynaptic membrane is the presynaptic grid characterized by dense-staining projections. These contain actin-like filaments and are thought to be vesicle-docking sites. The presynaptic vesicles congregate in the vicinity of the presynaptic grid though many also occur throughout the bouton (**Figure 4**; see also the images in the "chemical synapses" section of Josef Spacek's Ultrastructural Atlas on Synapse Web). The total number of vesicles in completely reconstructed axonal boutons ranges from 38 to 1234 for cerebellar spines and 3 to 1606 for CA1 spines. This number is proportional to spine and synapse dimensions. Some of the boutons also contain a few dense core vesicles, whose composition have not been thoroughly described at spines, but may include adrenergic neurotransmitters, growth factors, or other neuropeptides. Recent ultrastructural studies combined with electrophysiological studies suggest that variation in vesicular size, composition, and distribution with respect to the synaptic cleft reflects their state and whether they are in the midst of releasing

neurotransmitter, recycling, or held in reserve (**Harata et al., 2001**).

2.6. Synaptic cleft

Between the pre- and postsynaptic membranes is the synaptic cleft, a region where the extracellular space widens slightly to about 10 to 20 nm. This cleft is filled with a dense-staining material, which is thought to be comprised of cell surface molecules involved in cell-cell adhesion, such as integrin-like and neural cell-adhesion molecules, and in molecules such as agrin that are involved in synaptic receptor localization (**Südhof** TC)

2.7. Neighboring astrocytic processes

In most brain regions at least some of the dendritic spines occur in close association with tiny astrocytic processes. This association ranges from a complete surrounding of the synaptic complex, seen at cerebellar dendritic spines, to the less conspicuous interdigitation of astrocytic profiles amongst synapses in the hippocampus (**Figure 5**; **Ventura and Harris, 1999**). Astrocytes are important both for energy metabolism at synapses (only astrocytes actually store glycogen) and in controlling the extracellular concentrations of glutamate. In these ways, astrocytes have a direct role in normal synaptic transmission and preventing glutamate mediated excytotoxicity.

3. Functions of dendritic spines

3.1. Postsynaptic targets

Evaluation of dendritic spine structure readily reveals them to be the major postsynaptic target of excitatory synaptic input. Since most dendritic spines have a single excitatory synapse on their head, more spines means more synapses and accordingly more point-to-point connections in a neuronal ensemble involving spiny neurons. Thus, one function of spines is the preservation of the individuality of inputs. Occasionally inhibitory or modulatory axons also form synapses on the heads, necks or at the bases of dendritic spines. An inhibitory input on spines could act to "veto" or modify the strength of the excitatory input.

3.2. Expanded reach to presynaptic axons

It had been postulated by Ramon y Cajal that spines could increase the surface area available for new synapses to form. Serial EM reconstructions show, however, that most of the dendritic surface between spines does not have

synapses, and ample room is available for more synapses to occur even in the absence of more dendritic spines. Spines do allow relatively thin dendrites to reach multiple axons as they weave through the neuropil. For nonspiny dendrites to attain the same reach to the meandering axons they would need to be thicker than spiny dendrites (which typically they are), and to occupy a significantly greater volume of the neuropil. Thus, spiny dendrites allow more synaptic connections to be compacted into a limited brain volume.

3.3. Amplification of voltage in spine head

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The constriction in dendritic spine necks, poses a small resistive barrier thereby amplifying the depolarization attained in the immediate vicinity of the synapse, in contrast to that which would be generated if the synapse occurred directly on the wide dendritic shaft. Computer simulations have revealed that most of the spine necks are sufficiently wide and short that charge transfer to the postsynaptic dendrite is 85% to 100% complete within 100 ms after the initiation of a synaptic event. The time delay in charge transfer is sufficient, however, to provide a transient amplification of voltage at the spine synapse which may facilitate opening of voltage-dependent channels in the spine head, such as the calcium-channel associated with the NMDA class of glutamate receptors.

3.4. Sharing of postsynaptic potential

A long-standing hypothesis has been that the narrow dimensions of the spine neck would attenuate current flow between the spine head and the dendrite. Morphological evidence suggests, however, that most spine necks are not thin and long enough to reduce, significantly, the charge transferred to the parent dendrite. Current electrophysiological evidence from hippocampal CA1 cells suggests that the mean synaptic conductance for a minimal evoked response is 0.21 ± 0.12 ns, such that the current generated by release of 10 to 20 quanta would likely be fully transmitted to the postsynaptic dendrite. Thus the constriction in the spine neck is not sufficient to prevent addition of voltage changes amongst co-activated synapses. Other models endow the spine with active membrane that would further enhance the sharing of postsynaptic potentials among neighboring spines.

3.5. Biochemical compartmentalization

Compartmentalization of calcium has now been demonstrated in the heads of dendritic spines under a variety of conditions (**Sabatini, Maravall, and**

Svoboda, 2001). Two features of spines help to achieve localization of this second messenger in spine heads at least for a short time: (1) the spine neck could provide a narrow diffusion path; and (2) a rise in spine calcium could cause release from SER, the intracellular calcium stores thereby amplifying the calcium signal. Biochemical compartmentalization in spine heads may also serve an important role in restricting calcium from the postsynaptic dendrite, thereby preventing excitotoxic cell damage such as microtubule breakdown and mitochondrial swelling. Since dendritic spines rarely have microtubules or mitochondria, high calcium concentrations in the spine head is less likely to have these detrimental effects.

Not all spine morphologies would be expected to restrict diffusion, and only a subset of spines has internal stores. Perhaps only a subset of spines, or alternatively all spines, but only at a restricted time during their history, achieve the compartmentalization of calcium, whether in spines or along a short segment of dendrite and its associated spines. The specific localization of voltage-dependent calcium channels is also an important factor in determining which components of the dendritic arbor will compartmentalize and utilize relatively high concentrations of calcium. Whether spines preferentially sequester other second messengers remains to be determined. Certainly those tethered to the PSD are prevalent in spines, but further work is needed to determine how they are targeted to spines and whether compartmentalization in the spine head is a crucial element in their regulation.

4. Structural synaptic plasticity at dendritic spines

Several mechanisms could mediate rapid short term and long term changes in spine and synaptic morphology (Yuste and Bonhoeffer, 2001). Glutamate and its analogues activate proteolysis of brain spectrin (fodrin), a structural protein of the (spine) cytoskeleton, thereby possibly allowing the spine to undergo shape changes in response to growth of the synapse. Depending on age, spines can also stabilize in response to activation. Different pools of actin filaments are transient or stable and respond differentially to the calcium-activated second messenger systems following synaptic transmission (Halpain, 2000; Matus, 2000).

Recent studies suggest that spines undergo changes in structure with synaptogenesis during development, during behavioral changes associated with learning and memory, and under pathological conditions associated with neural dysfunction. Long-term potentiation (LTP) is a cellular model of learning and

memory that has been extensively investigated regarding changes in spine and synapse structure. Two key structural changes would contribute to a potentiated synaptic response, an increase in the number or an increase in the size of synapses with LTP. Although there is considerable controversy in this field, especially as concerns structural plasticity in the mature brain during LTP, the results from immature neurons are more consistent. Namely, new dendritic protrusions form (reviewed in **Yuste and Bonhoeffer, 2001**) and make synapses with pre-existing axons (**Fiala, Allwardt, and Harris, 2002**) after stimulation that induces LTP. In adult hippocampus, no change in synapse number or size has been identified during LTP. The apparent stability in synapse number and size in the mature hippocampus might not be a result of no change, but instead there might be an increase with a parallel down-regulation at adjacent synapses not undergoing LTP so that no overall change is detected. The plausibility of this hypothesis is supported by complementary findings in the mature brain. If synaptic transmission is blocked for several hours in vitro, mature hippocampal neurons are seen to acquire many new dendritic spines, as though they are trying to compensate for the loss of synaptic input (**Kirov and Harris, 1999**).

Findings from somatosensory cortex show that enhanced activation of a single whisker can result in a short-term increase in both excitatory and inhibitory synapses on dendritic spines (**Knott et al., 2002**). Over the long term the excess excitatory synapses regress, but the inhibitory synapses remain as second synapses on dendritic spines. Electrophysiological studies from the same neurons show that the extra inhibitory synapses serve synaptic potentiation at a delay. The first response is reduced, but the delayed second response is potentiated. It is clear that the interplay between excitatory and inhibitory synapses on spine structure and connectivity will provide important new insights into how synaptic circuits can become potentiated, depressed, or otherwise altered during experience and memory.

5. See also

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Dendrites, dendrodendritic interactions
Dendrites, physiology
Dendritic spines, pathology and changes with age
Synapse, postsynaptic density
Synaptic plasticity
Synapse, morphology

Postsynaptic mechanisms

6. Further reading

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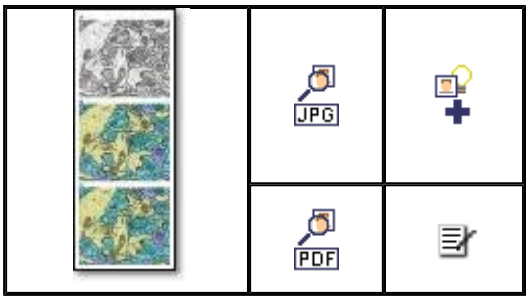
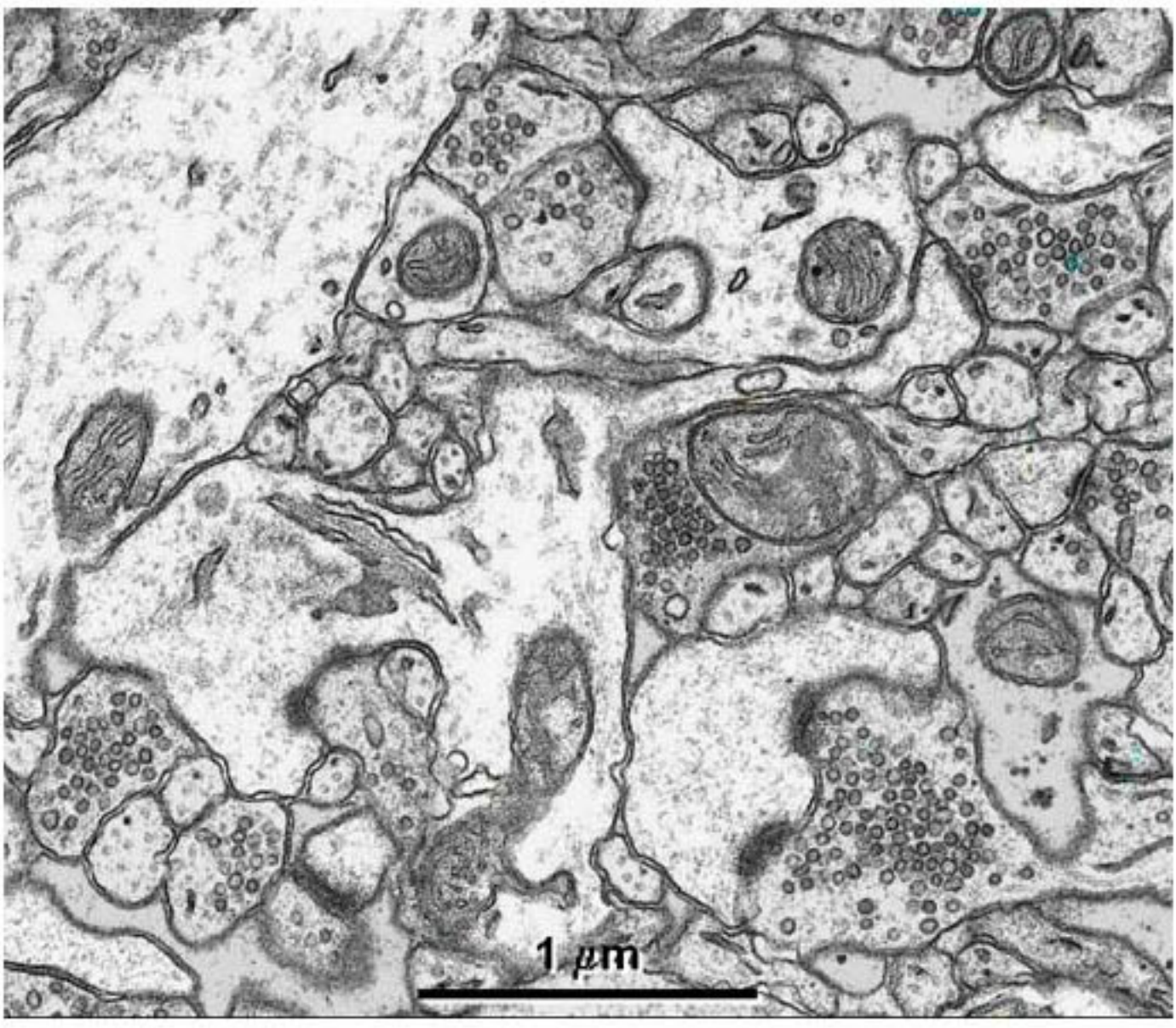


Figure 1. Electron micrograph of a section through dendritic spines in stratum radiatum of hippocampal area CA1. In this fortuitous section, three spines were sectioned parallel to their longitudinal axis revealing spines of the stubby (S), mushroom (M), and thin (T) morphologies. The postsynaptic density (PSD) occurs on the spine head (see T) immediately adjacent the synaptic cleft (c) and

the to a presynaptic axonal bouton that is filled with round vesicles (v). This T spine contains a small tube of smooth endoplasmic reticulum (ser) in its neck. In the M spine a spine apparatus (SA) is visible. A perforated postsynaptic density (pf) is evident on the head of another mushroom spine. Near to this spine is a large astrocytic process (A) identified by the glycogen granules and clear cytoplasm.

A



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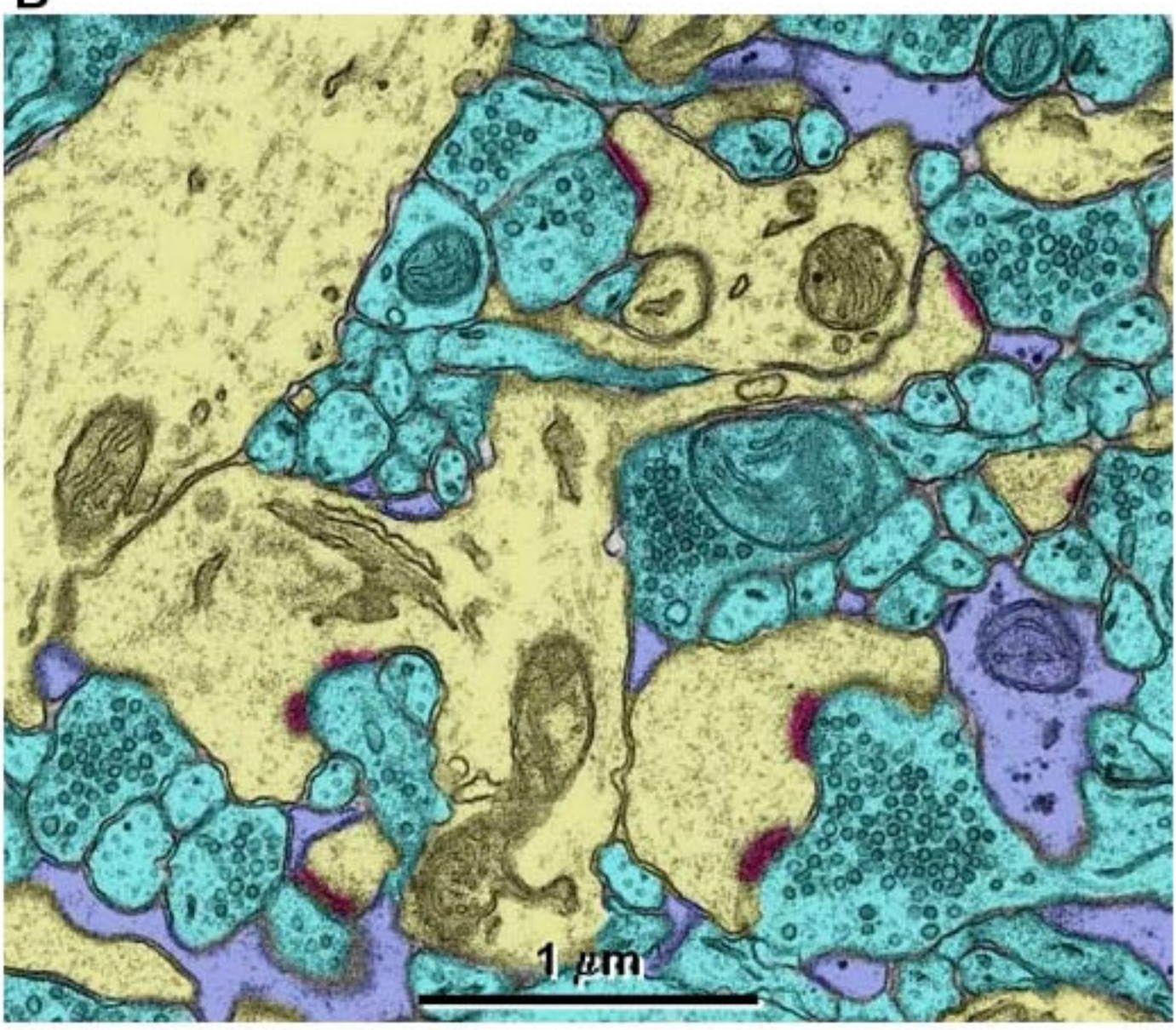

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