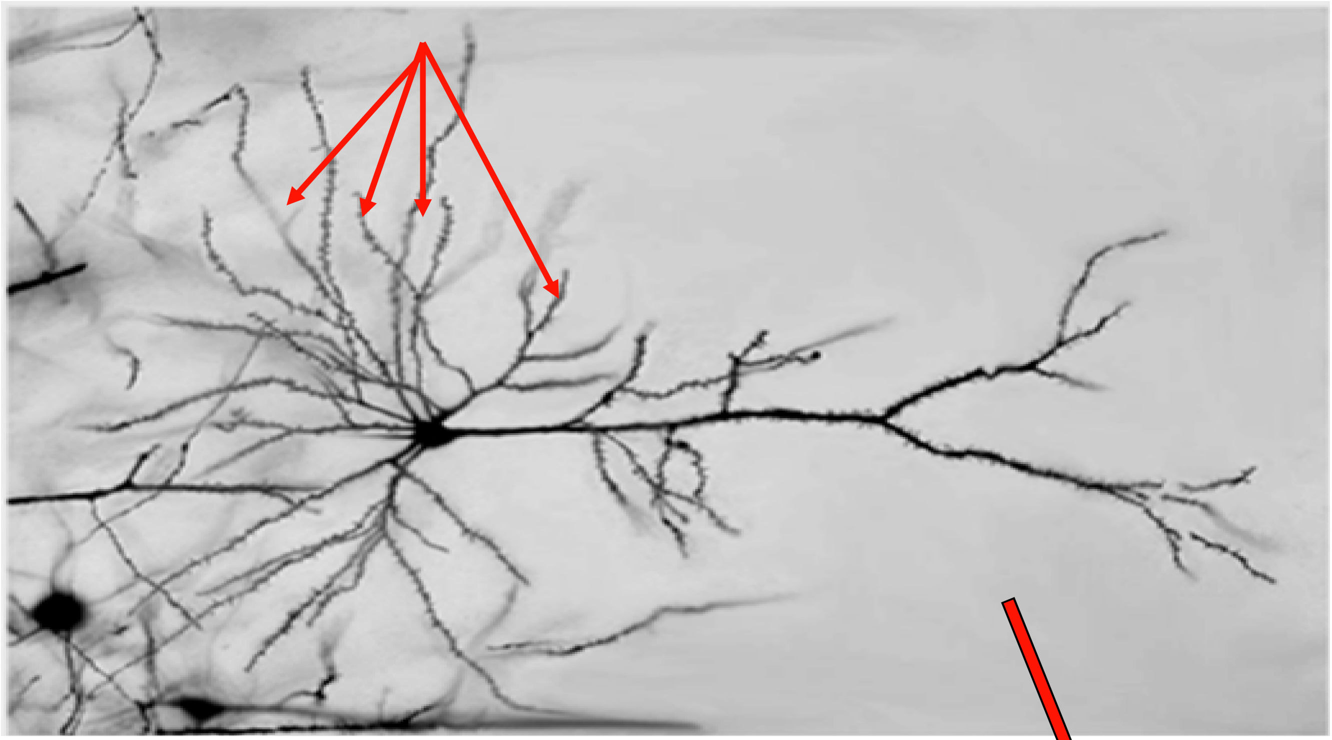
Lesson (5)

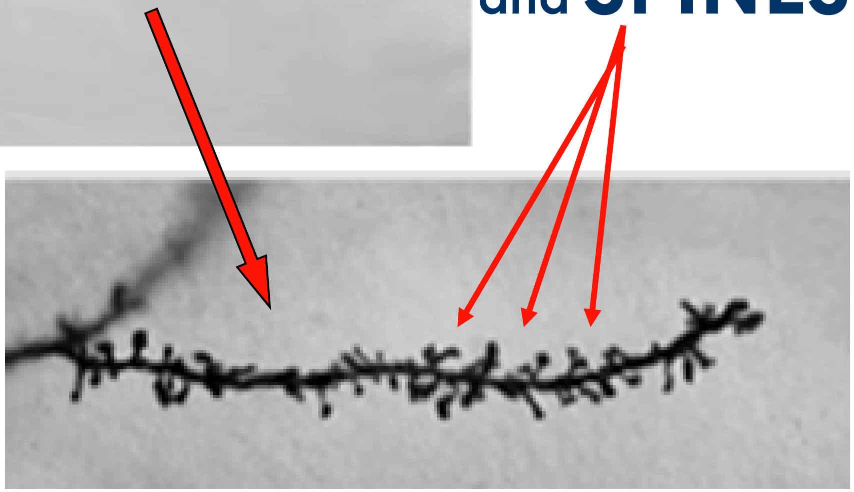
Inside the neuron I: Dendritic Spines

NEURON

DENDRITES

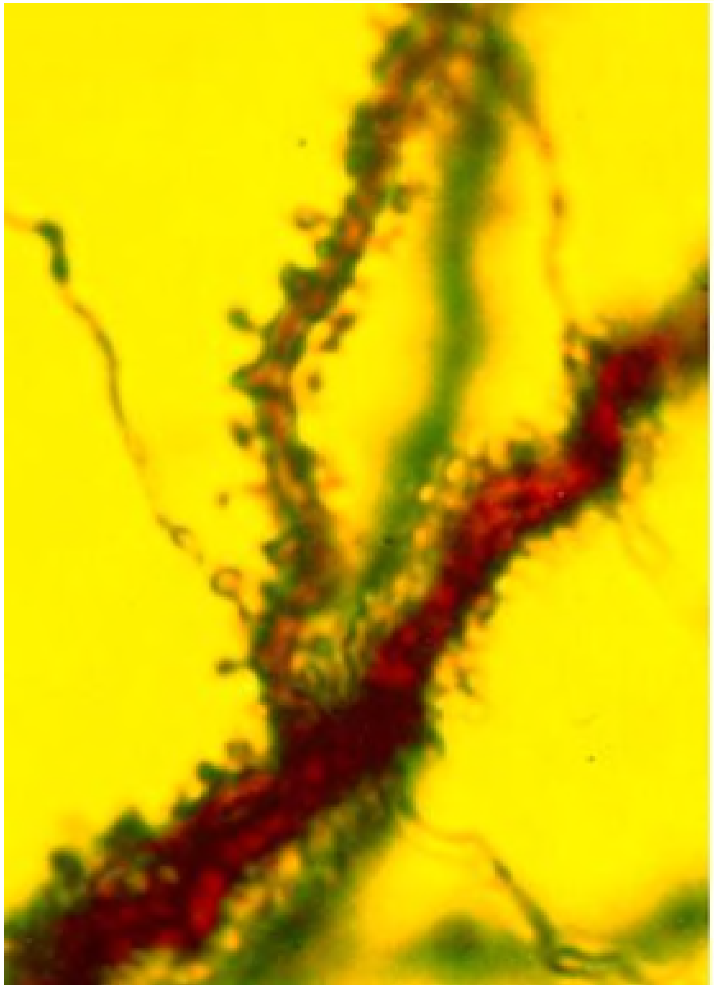


and SPINES



Several neurons show dendritic spines

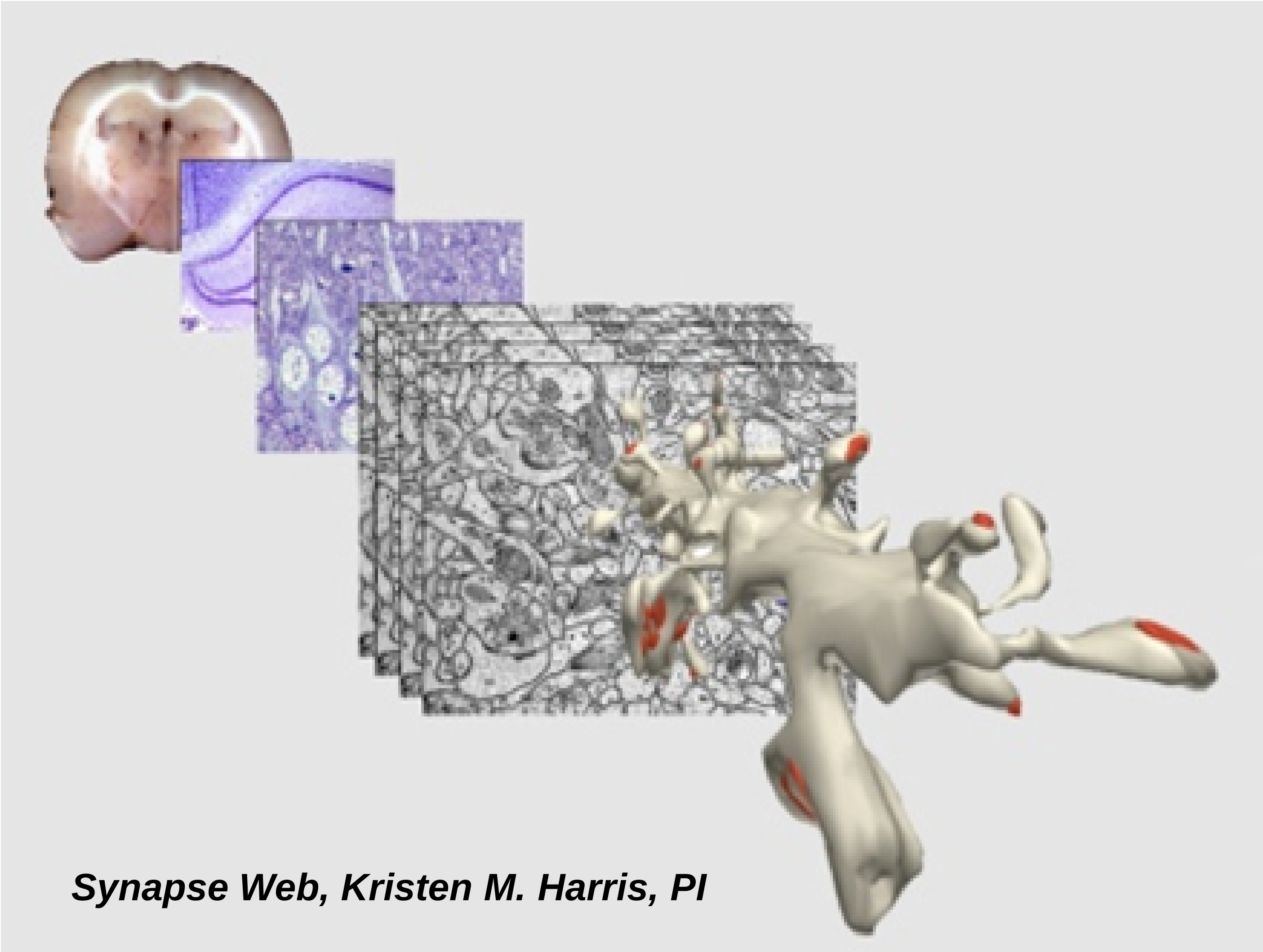
DENDRITIC SPINES



Synapse Web, Kristen M. Harris, PI

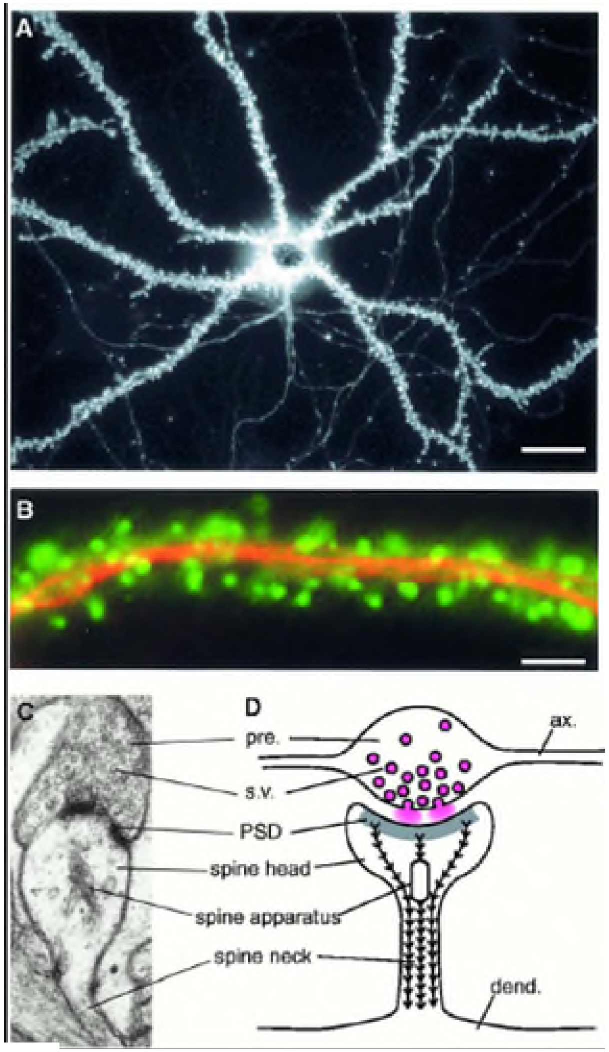
A tridimentional reconstruction from electron microscopy images

3D reconstructions of EM pictures of spines

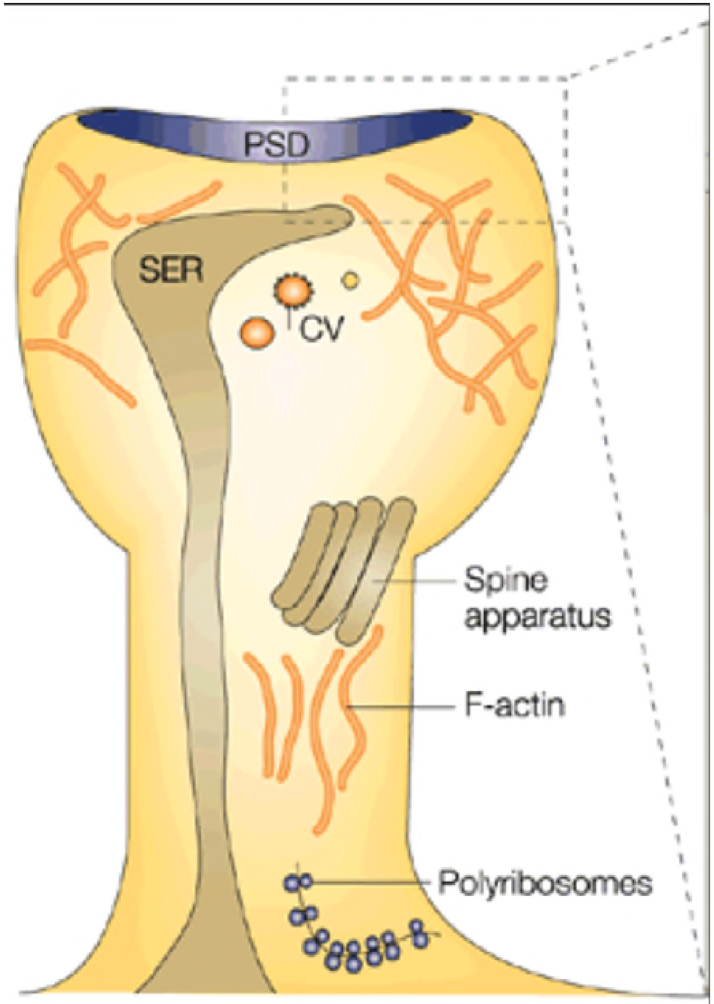


https://www.youtube.com/watch?v=8YM7-Od9Wr8

Dendritic spines: what is inside?



Sala el al. Neuron 2001



Hering and Sheng 2001

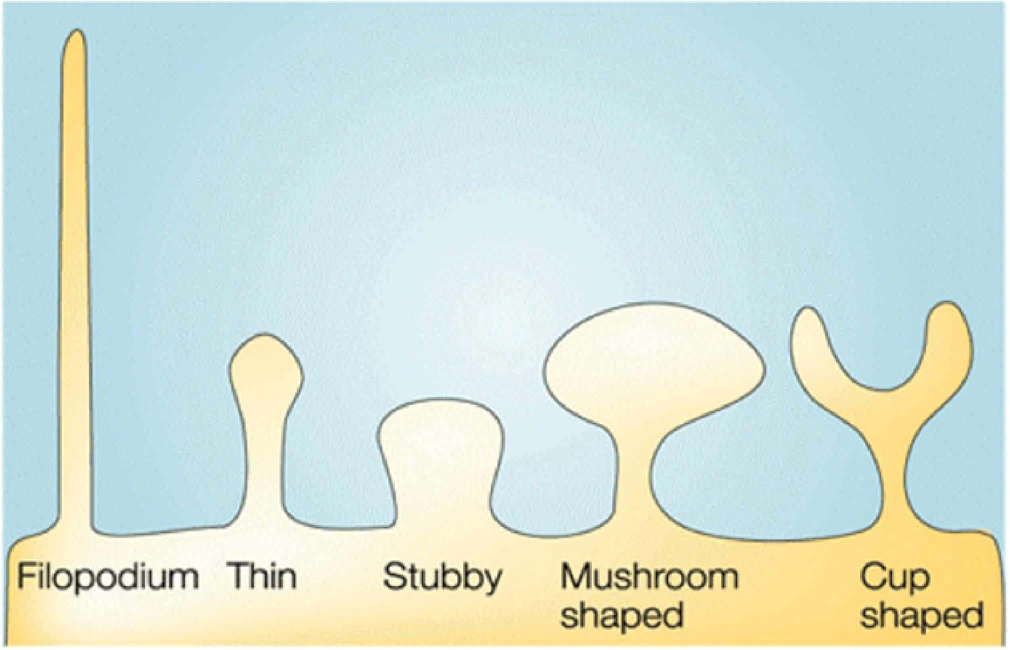
Dendritic spines types

Ultrastructural studies have traditionally classified spines into major categories based on their distinct morphologies:

- stubby,
- thin,
- mushroom

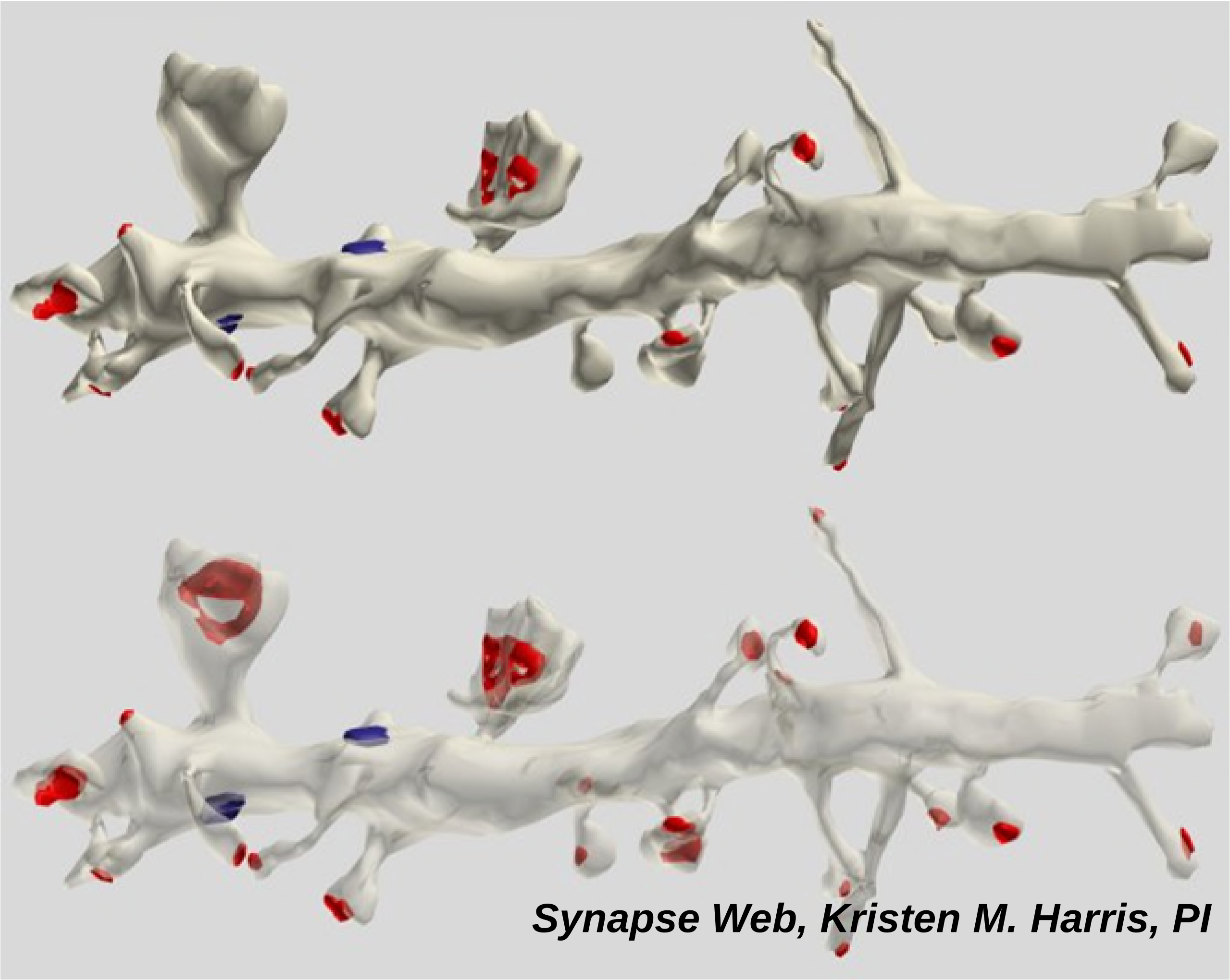
The number and shape of dendritic spines are highly mutable on time scales ranging from seconds to days, suggesting that several different intrinsic mechanisms control spine dynamics.

DENDRITIC SPINES



Nature Reviews | Neuroscience

Hering and Sheng 2001



A segment of pyramidal cell dendrite from stratum radiatum (CA1) with <u>thin, stubby, and mushroom-shaped spines</u>.

http://synapses.clm.utexas.edu/

Thin dendritic spine **(*S*) with axo-spinous synapse.**
D - dendritic stem.

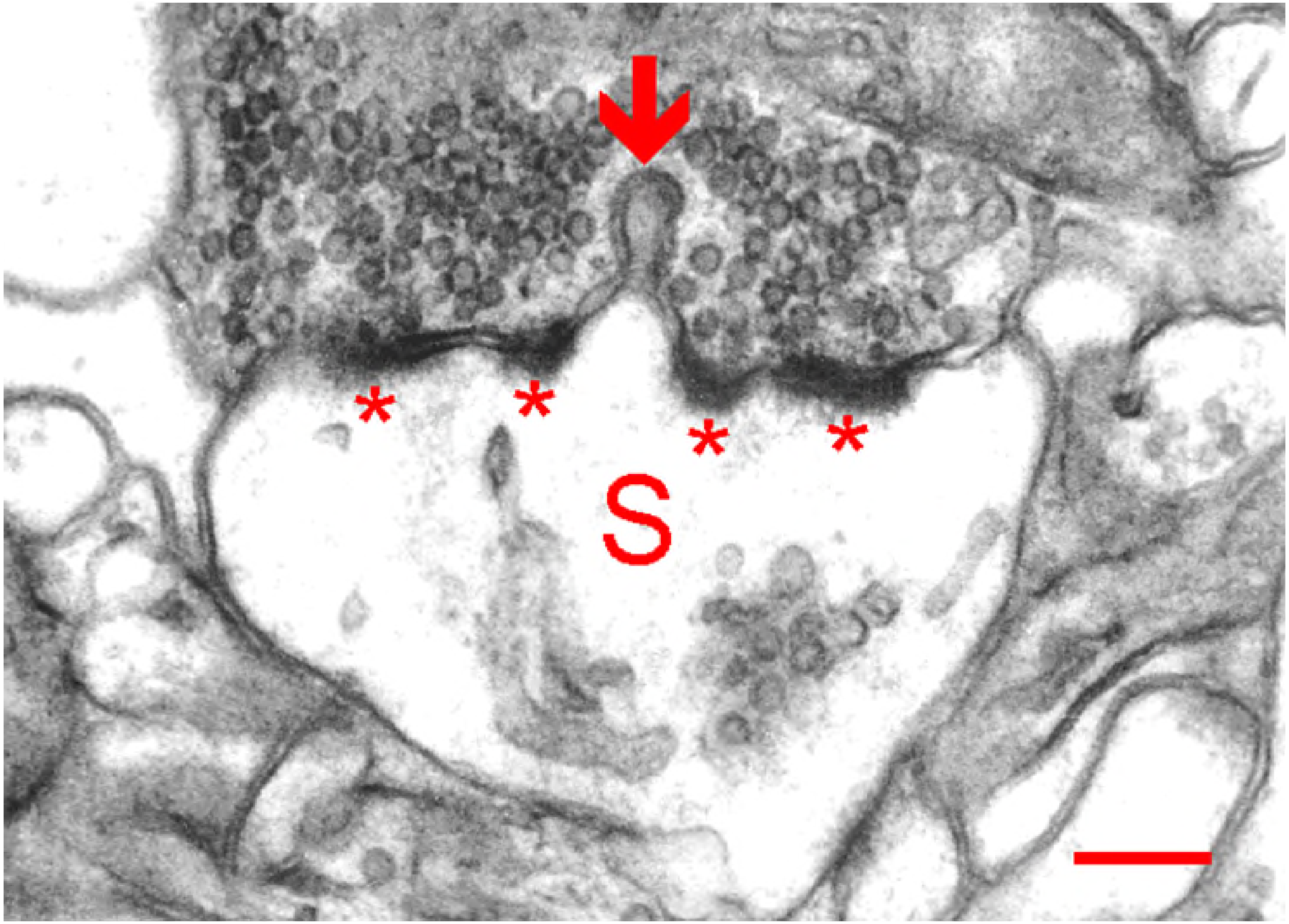
from "Atlas of Ultrastructural Neurocytology"

Stubby dendritic spine (*S*) with axo-spinous synapse. *Microtubule* labeled by arrow

from "Atlas of Ultrastructural Neurocytology"

Mushroom-shaped dendritic spine **(s) containing a** ***spine apparatus*** **(arrow) in its head. D**

from "Atlas of Ultrastructural Neurocytology"

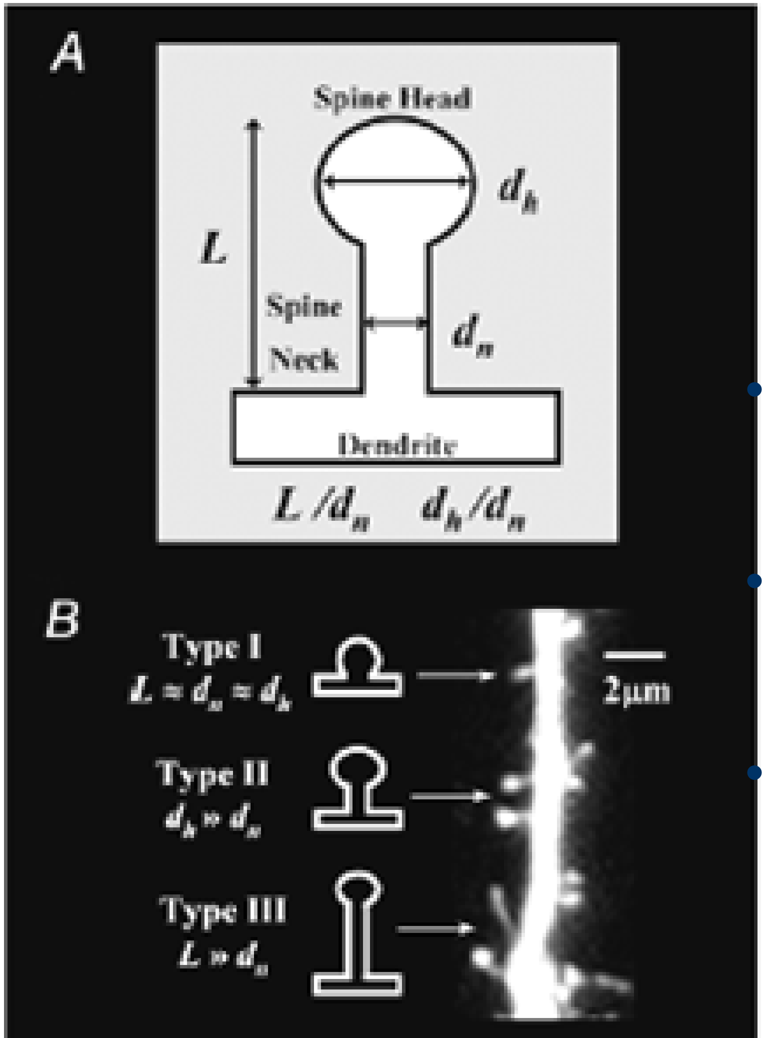


The head of a *mushroom-shaped dendritic spine* (*S*) with a *spinule* (arrow) protruding into the presynaptic axon terminal

from "Atlas of Ultrastructural Neurocytology"

Dendritic spines

Classification of spine categories



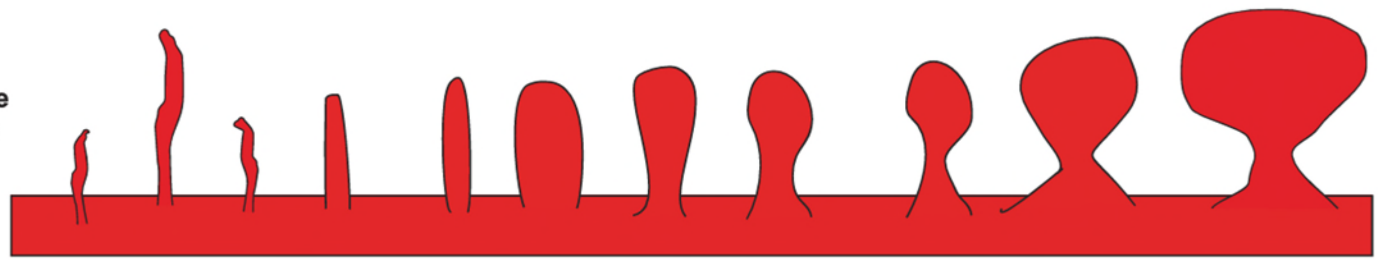
Dendritic spines were classified using the length (*L*), neck diameter (*d*n) and head diameter (*d*h) of individual spines

- TYPE I : stubby spines,
- TYPE II : mushroom spines
- TYPE III : thin spines,

In real world: a continuum of spine shapes and sizes

A

	Filopodia like structures	Immature Spines	Mature Spines
Continuum of spine shapes and sizes			



B

Dynamic	Extremely[1,2]	Very[1,3-7]	Rarely[1,3-6,8]
Average Lifetime	Minutes to hours[2]	~2 days[4]	> 1 year[1,4]

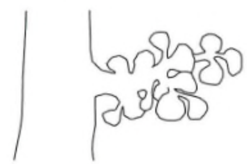
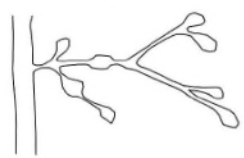
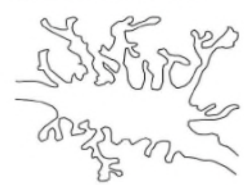
C

Prevalence	~2-3% in mature brain ~10% at 1 month old >25% early postnatal[1,9]	~20% of spines in young adults presumeably more in development[3-6]	~70-80% of spines[1,3-6,8]

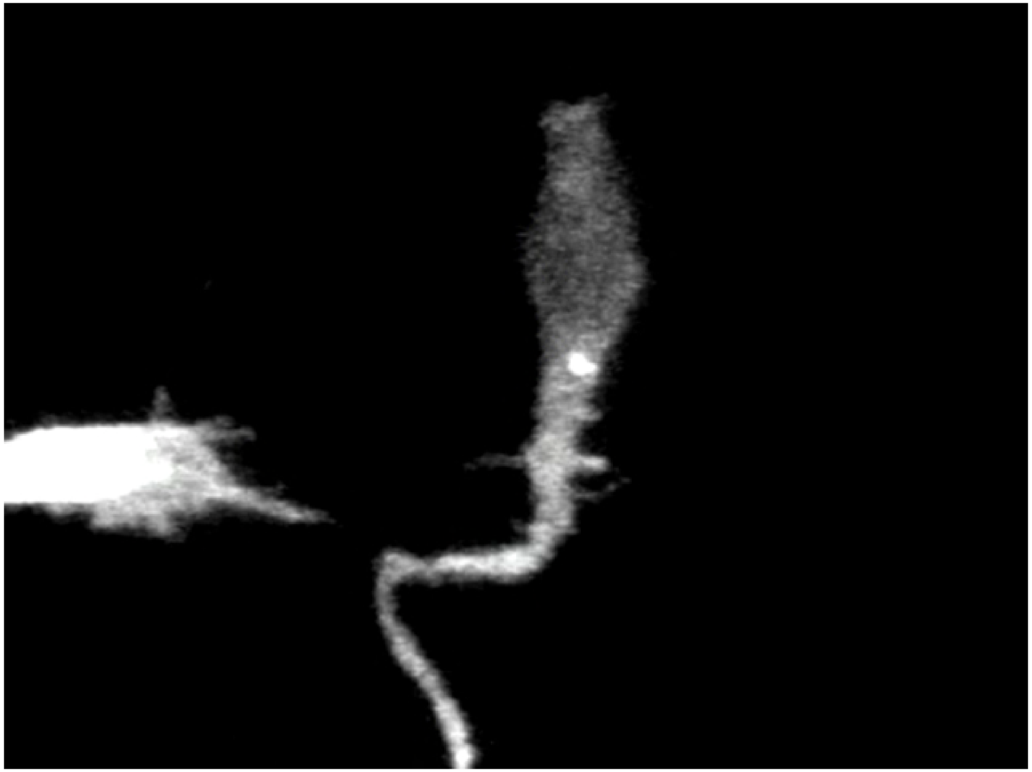
Berry and Nedivi, 2017

OTHER DENDRITIC SPINES TYPES

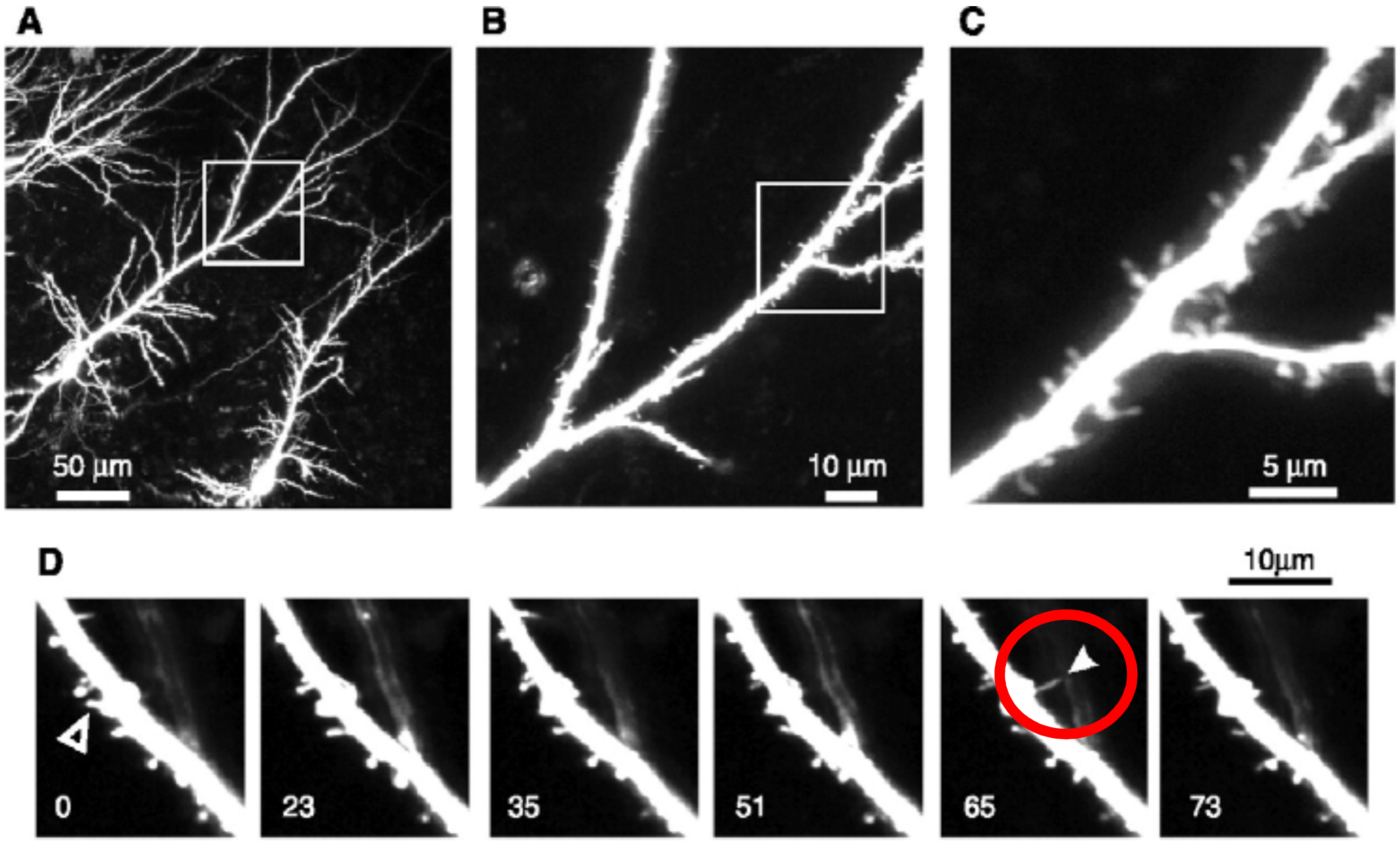
Table 1.3 Synaptic specializations of dendrites

Pattern	Characteristics	Examples
Varicosity 	An enlargement in a thinner dendrite associated with synaptic contacts	Retinal amacrine cells
Filopodium 	A long, thin protrusion with a dense actin matrix and few internal organelles	All neurons during developmental synaptogenesis
Simple spine Sessile 	Synaptic protrusions without a neck constriction	
	Sessile spine	Cerebral pyramidal cells
	Stubby spine	Cerebral pyramidal cells
	Crook thorn	Neurons of dentate nucleus
Pedunculated 	Bulbous enlargement at tip	
	Thin spine	Cerebral pyramidal cells
	Mushroom spine	Cerebral pyramidal cells
	Gemmule	Olfactory bulb granule cell
Branched spine 	Each branch has a unique presynaptic partner and each branch has the shape characteristics of a simple spine	CA1 pyramidal cells Granule cells of dentate gyrus Cerebellar Purkinje cells
Synaptic crest 	Crest-like protrusion with a synapse on either side of a thin lamellar neck region	Cerebral pyramidal cells Neurons of habenula, subfornical organ, and interpeduncular nucleus
Claw ending 	Synaptic protrusions at the tip of the dendrite associated with one or more glomeruli	Granule cells of cerebellar cortex and dorsal cochlear nucleus
Brush ending 	Spray of complex dendritic protrusions at the end of dendrite that extends into glomerulus and contains presynaptic elements	Unipolar brush cells of cerebellar cortex and dorsal cochlear nucleus
Thorny excrescence 	Densely lobed dendritic protrusion into a glomerulus	Proximal dendrites of CA3 pyramidal cells and dentate gyrus mossy cells Proximal dendrites of thalamocortical relay cells
Racemose appendage 	Twig-like branched dendritic appendages that contain synaptic varicosities and bulbous tips	Inferior olivary neurons Relay cells of lateral geniculate nucleus
Coralline excrescence 	Dendritic varicosity extending numerous thin protrusions, velamentous expansions and tendrils	Neurons of dentate nucleus and lateral vestibular nucleus

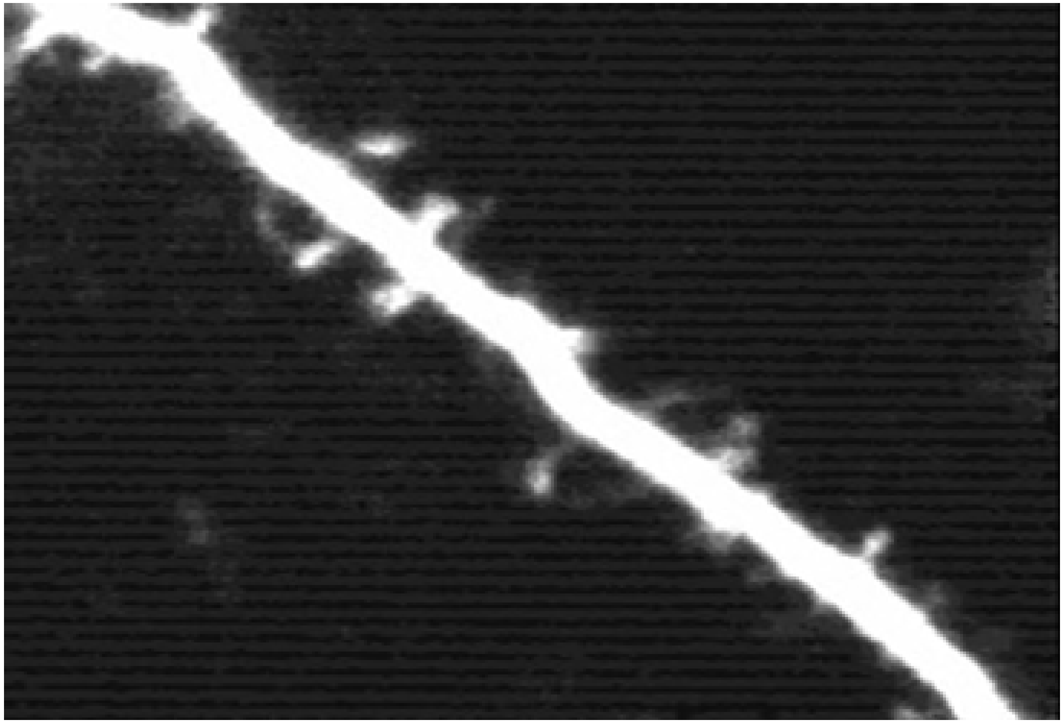
Spine and filopodia formation during development



Spine and filopodia formation during development



Spine and filopodia formation during development



The Disappearance of Filopodia Coincides with Appearance of Persistent Spines

Early stage

High number of filopodia

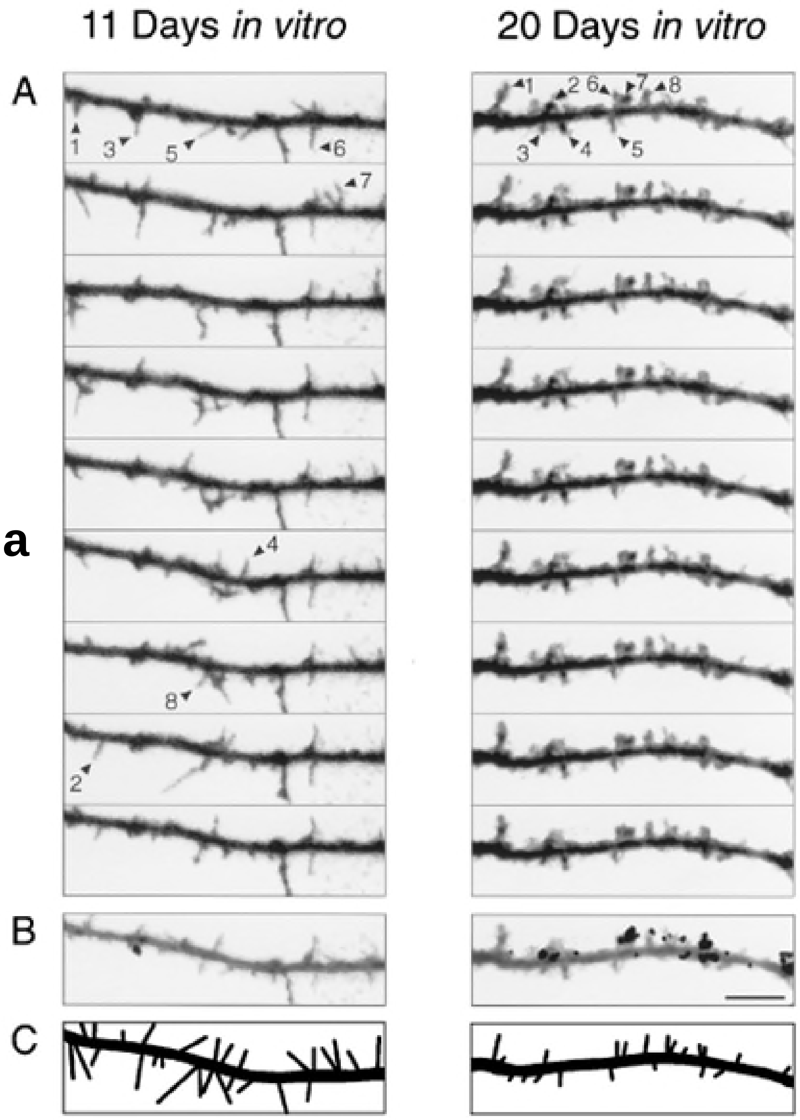


Figure 3. Time-Lapse Sequences of Dendritic Filopodia and Dendritic Spines

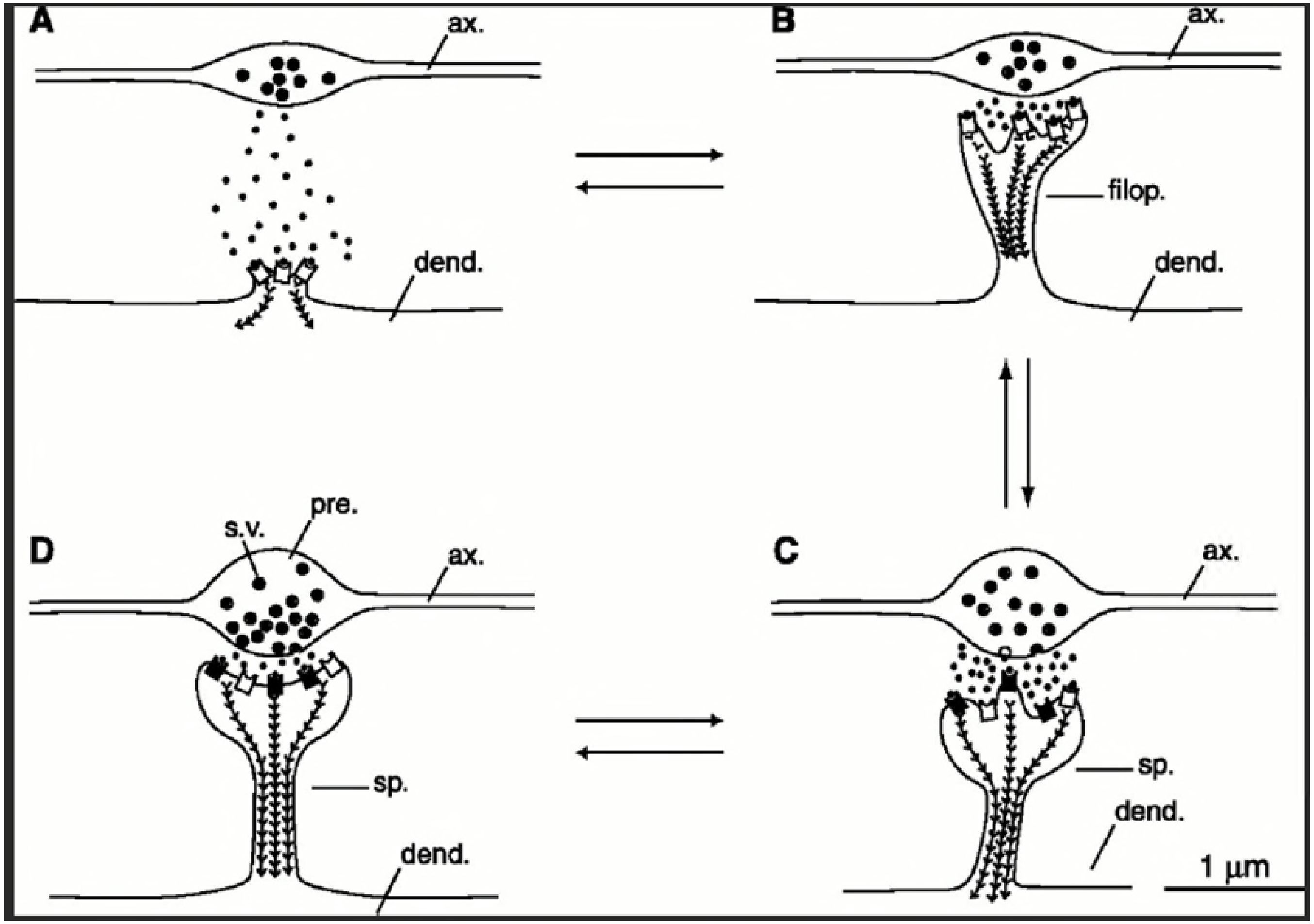
Mature stage

High number of spines

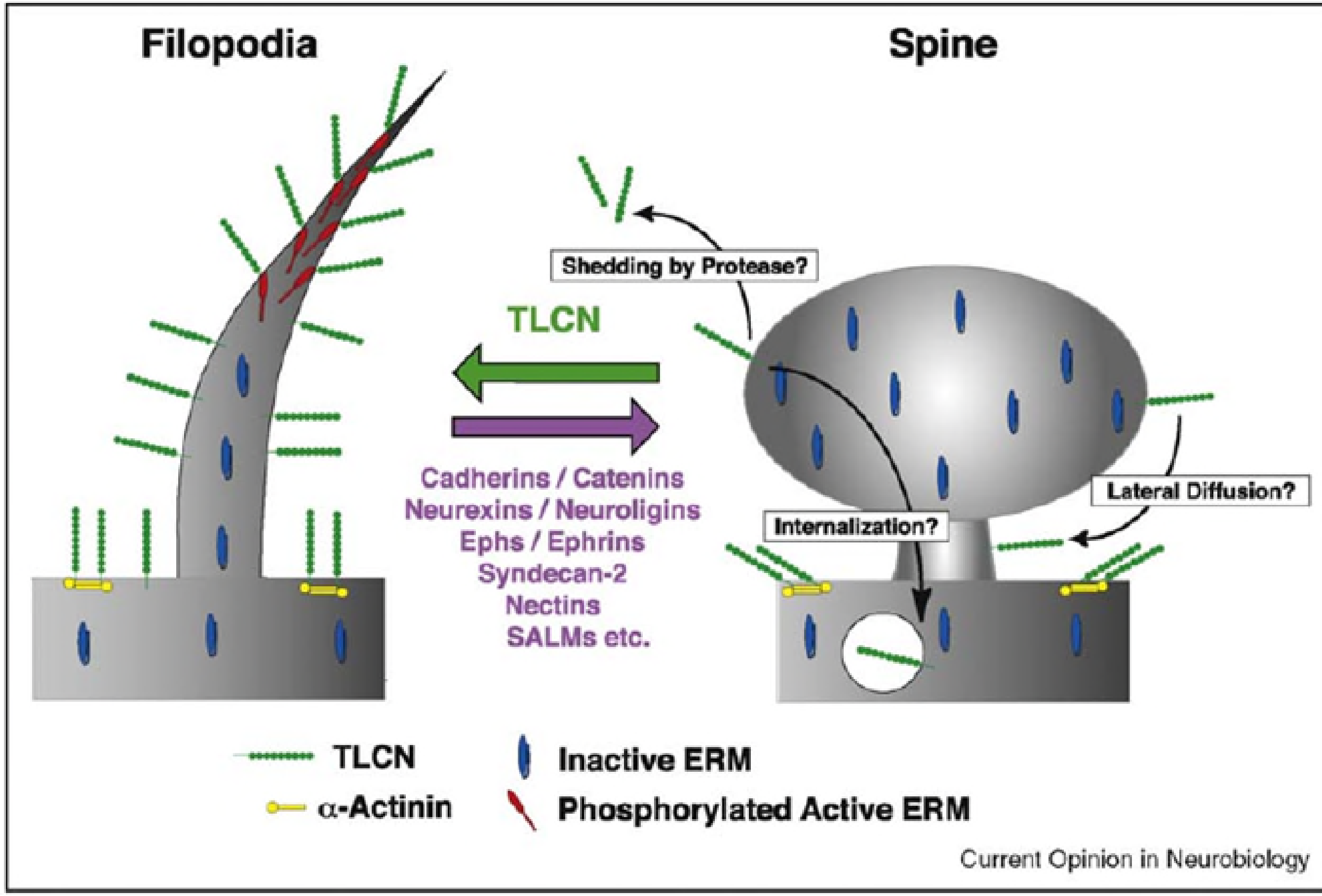
Ziv & Smith. Neuron, Vol. 17, 91–102, July, 1996,

Development of dendritic spines

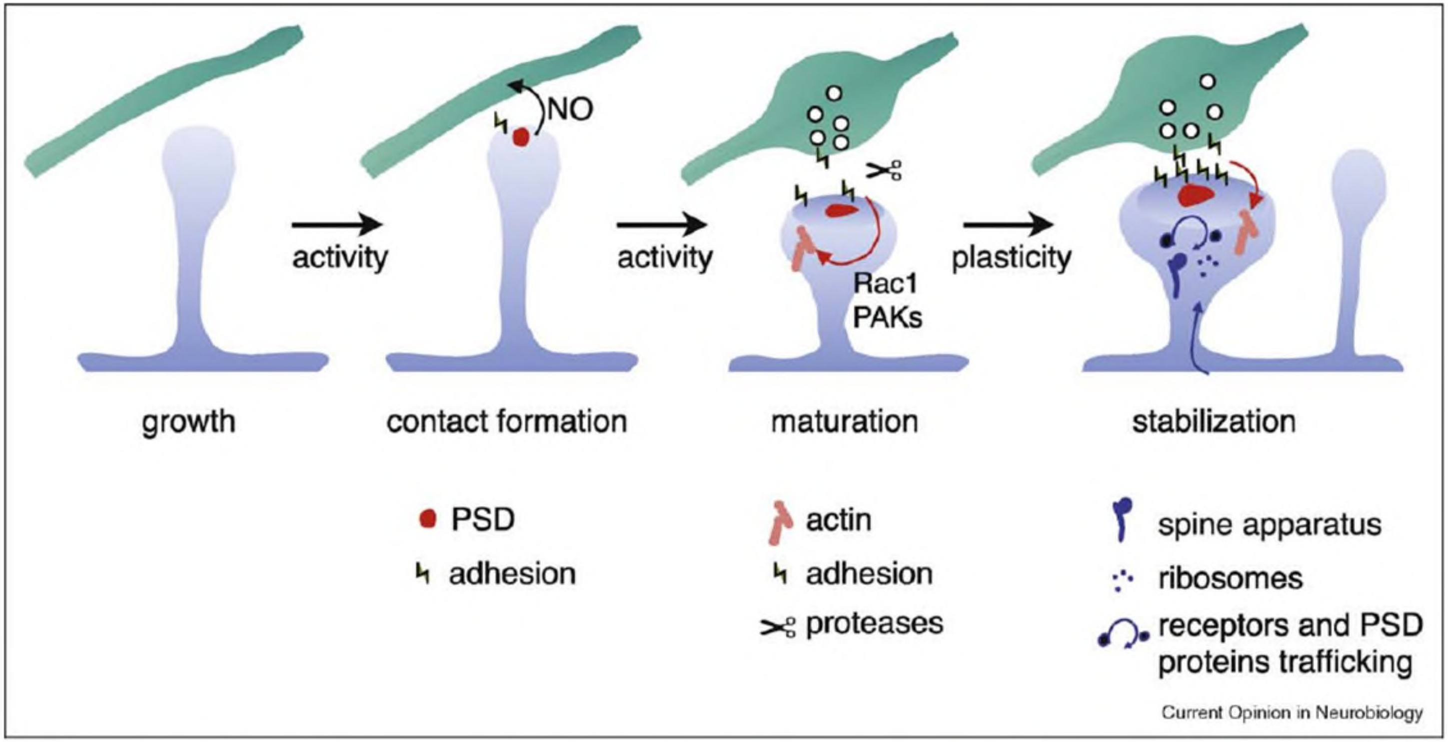
Dendritic filopodia transiently extend and retract from the dendritic shaft with an average lifetime of ~10 min to maximize the chance encounter between a developing axon and a target dendrite



Filopodia – Spine transition during development and plasticity

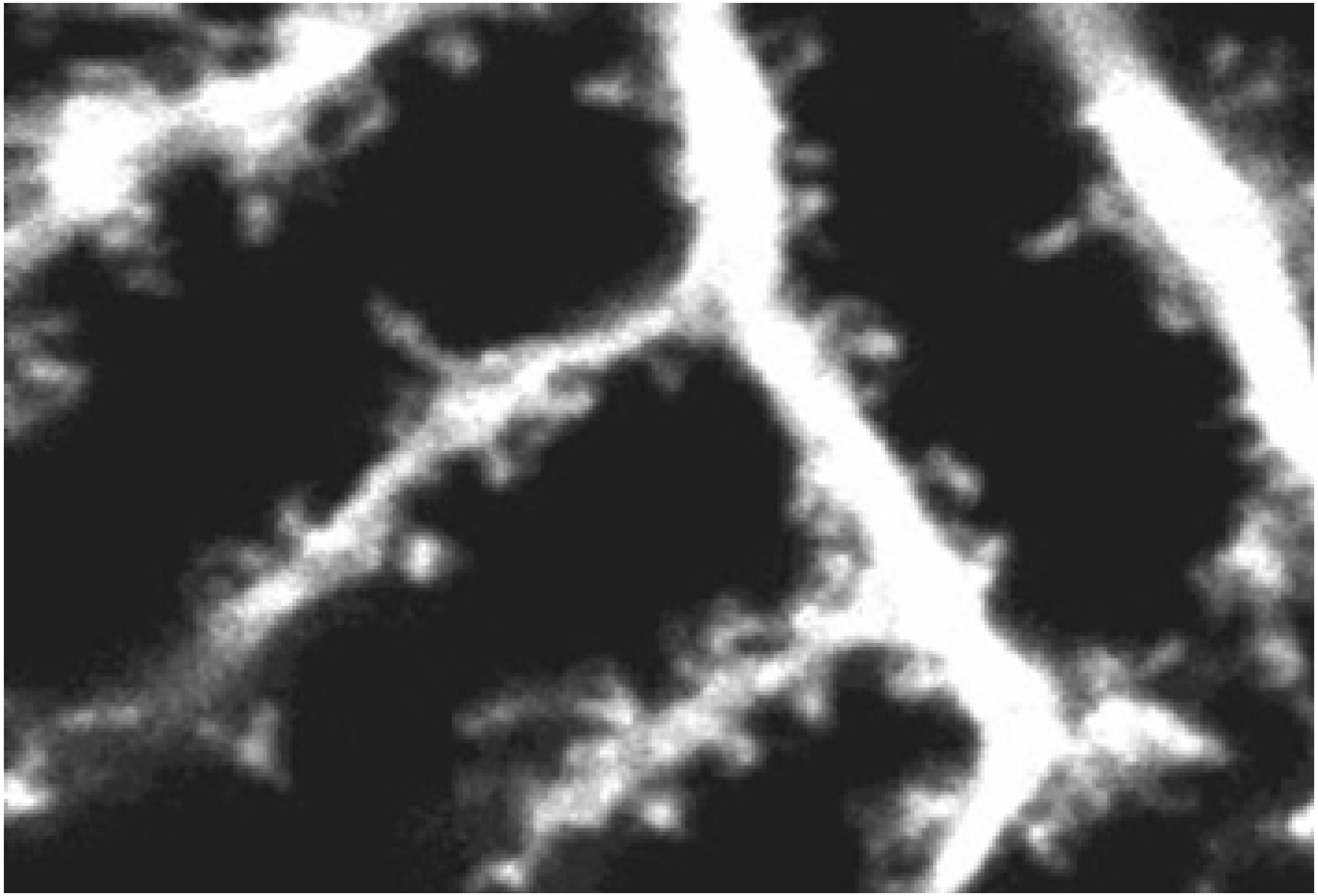


Putative molecular steps from spine growth to stabilization



A schematic diagram of putative molecular steps leading from spine growth to its stabilization. Current evidence suggests that newly formed spines initially grow without a PSD and a presynaptic partner. They might however rapidly express functional excitatory receptors, which, upon activation by ambient glutamate, could promote the formation of a PSD and through expression of adhesion molecules and retrograde signals such as NO promote presynaptic differentiation and contact formation. This process occurs within minutes to hours depending upon developmental stage or level of activity in the local environment. Functionality of the new synapse then ensures its maturation and enlargement through activation of multiple signaling pathways targeting Rho GTPases and regulation of the actin cytoskeleton. Long-term persistence of the spine might however require induction of synaptic plasticity, additional enlargement and acquisition of the machinery for protein synthesis.

Dendritic spines dynamics during plasticity



movie

Dendritic spines have dynamic changes especially during early development, but also during learning

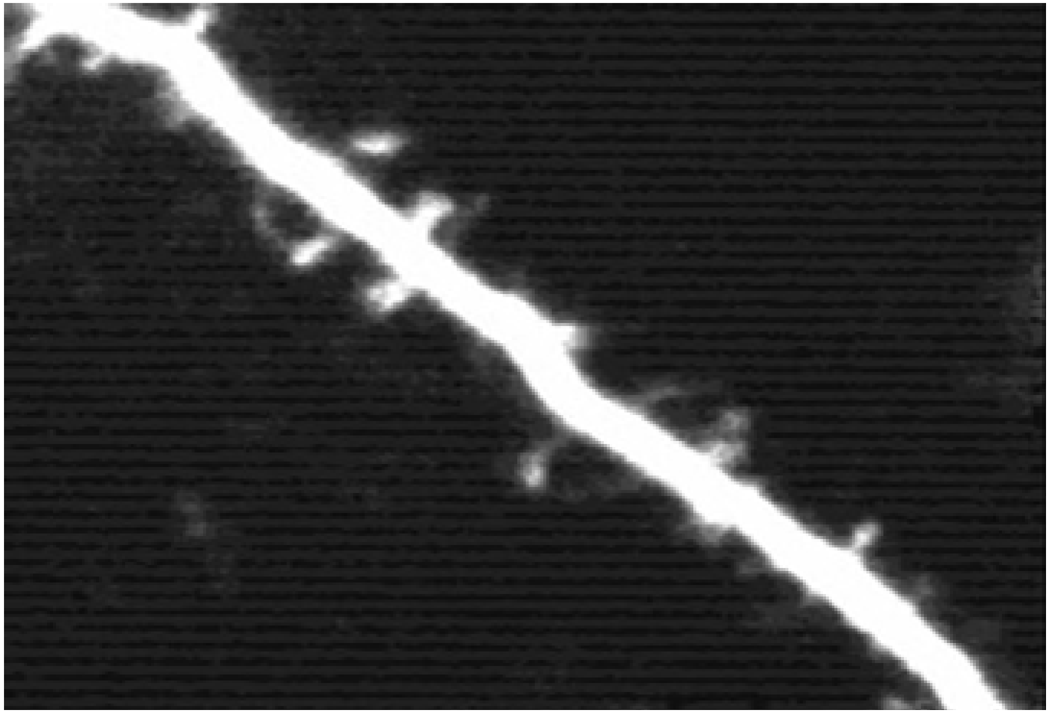
Learning and Memory

Neural activity plays an important role in the life history of dendritic spines by influencing the emergence of new spines, the stabilization of existing spines, and changes in spine morphology.

Complex phenomena such as learning involve both the genesis and retraction of dendritic spines that are region-specific and temporally restricted.

Dendritic spines changes in LTP

Changes in spine morphology have been observed following intense synaptic activity of the form that induces long-term potentiation (LTP), a persistent enhancement of synaptic strength that might underlie learning and memory.



movie

Spine dynamics

<u>The lifetime of newly formed spines falls into two groups:</u>

A) Spines that remain for months to years (when they disappear they never return)

B) Spine that are added and removed with a mean lifetime of ~2 days

2016). Transient spines tend to be smaller, but spines of all sizes and morphological subtypes from mushroom spines to filopodia can fall into either dynamic class (Holtmaat et al., 2005). The fraction of persistent versus transient spines varies with developmental age. In the mouse visual cortex and somatosensory cortex, only 35% of all spines persist at 3 weeks of age, increasing to 54% by 4–10 weeks and stabilizing at ~70% in the adult (Grutzendler et al., 2002; Holtmaat et al., 2005).

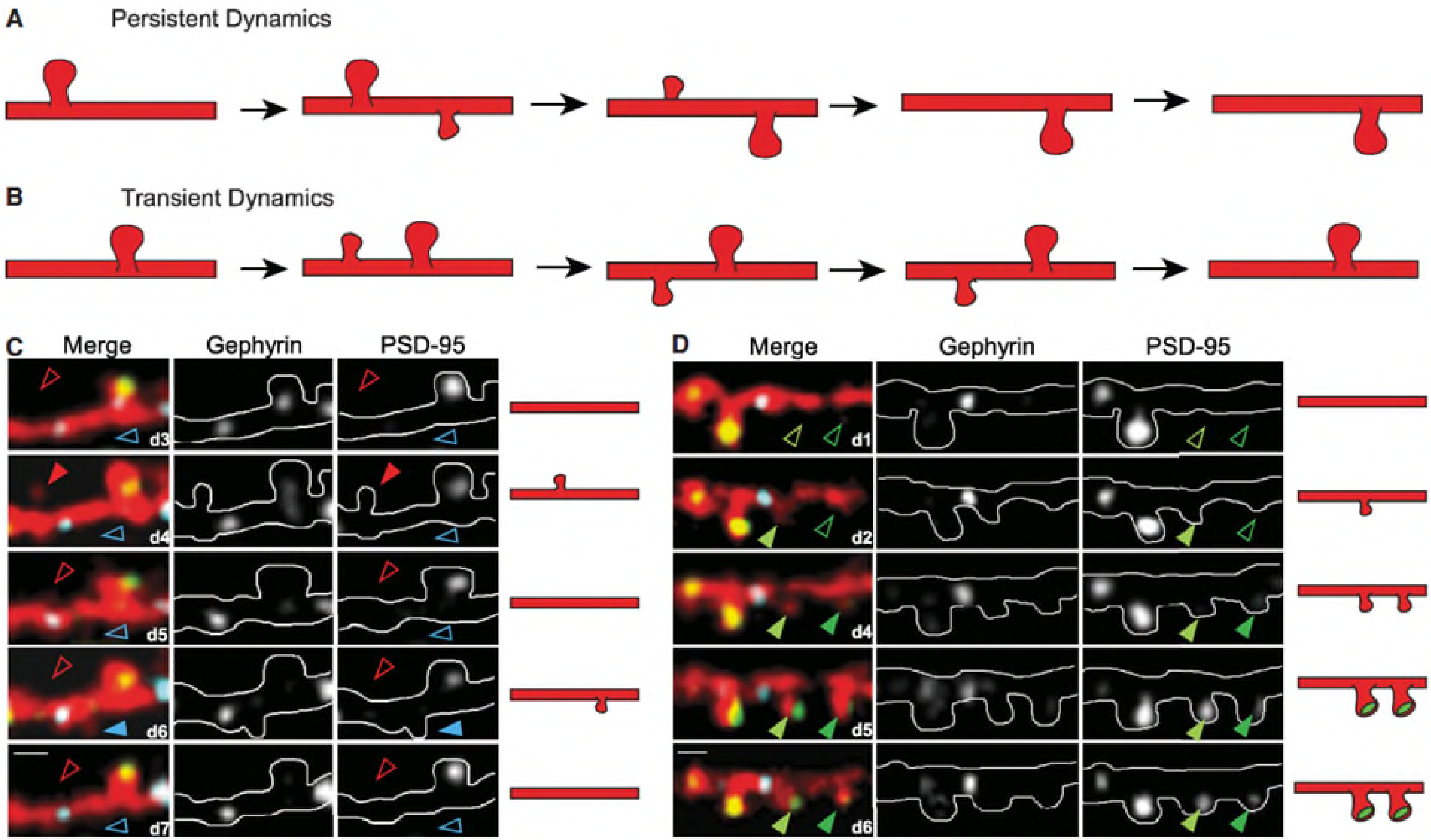


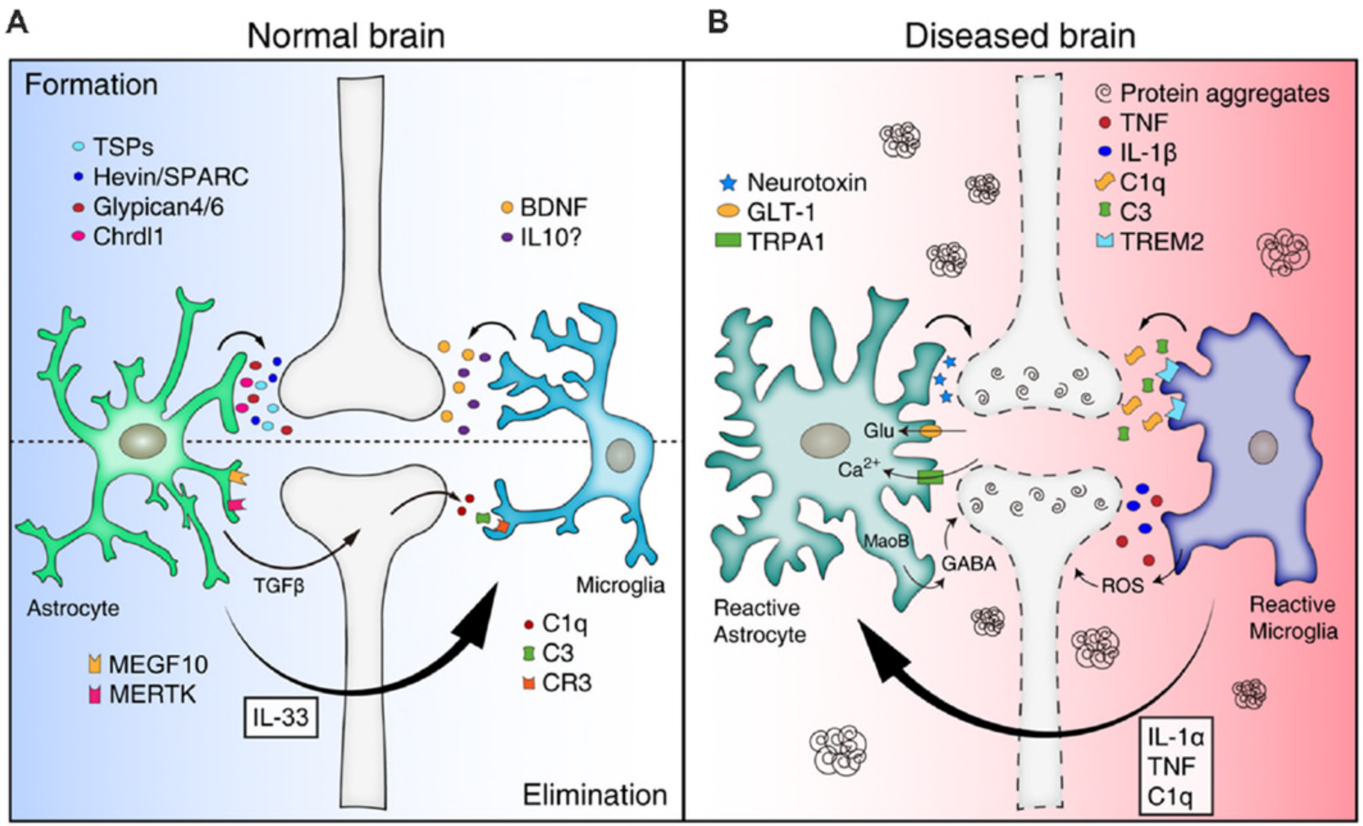
Figure 2. Dynamic Spines Fall into Either the Transient or Persistent Dynamics Categories

(A) Schematic illustration of two persistent dynamic events where a new spine forms and persists long term.

(B) Schematic illustration of two transient dynamic events that appear and disappear again with a few days.

(C and D) Examples of spine dynamics. Left, middle, and right panels show three-channel merge, Teal-gephyrin alone, and PSD-95-mCherry alone, respectively. Arrows denote dynamic spines: filled when spine is present and empty when spine is absent. (C) Shows the brief appearance and removal of spines without PSD-95 at separate nearby locations. (D) Shows formation of two new spines that gain a PSD-95 and persist. Adapted from Villa 2016).

Glial Control of Synapse Number in Healthy and Diseased Brain



What signals induce spine dynamics?

Spine density decreases naturally during normal aging

Hormonal status also can have a substantial impact on dendritic spines.

Among other factors, glutamate receptors and brain-derived neurotrophic factor (BDNF) have been implicated in activity-dependent synaptic remodeling

Spine Maintenance and Pruning

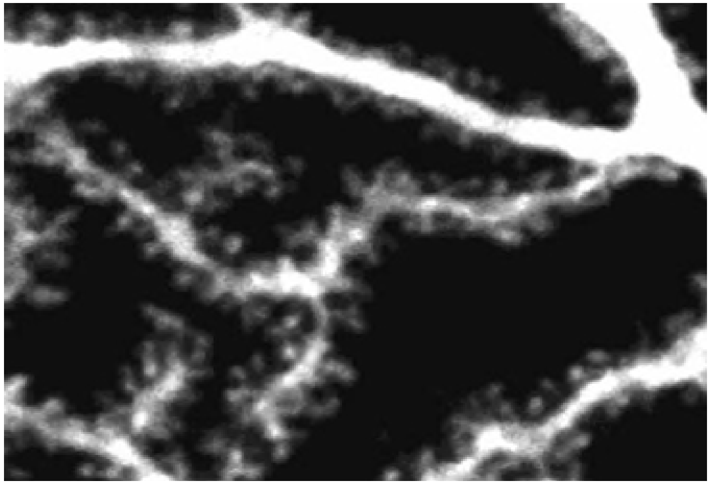
Once created, spines appear to require signals from their afferent neurons to remain intact.

In many brain regions spines initially are overproduced, and are then gradually and selectively eliminated in an activity-dependent manner during later development.

Potential functions of spine motility and dynamic actin include regulated protein scaffolding, retrograde signaling and synapse stabilization.

Regulation of dendritic spines motility

Motility is inhibited by blockers of synaptic transmission.
AMPA receptor activation causes the influx of Na+ ions through receptor-associated channels, postsynaptic membrane depolarization and spine motility.



Role of cytoskeleton in spine dynamics

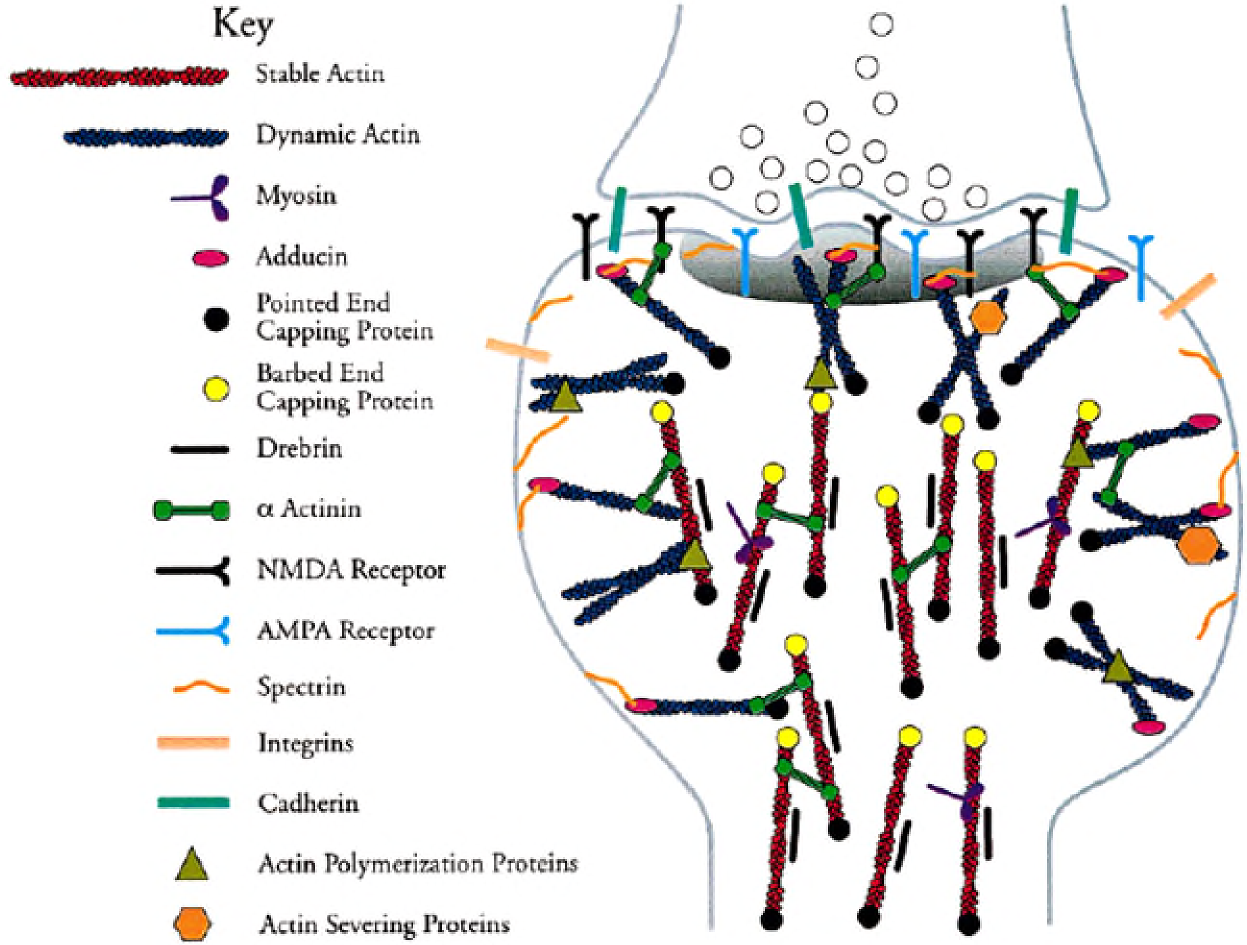
The spine cytoskeleton is based on actin filaments. Intermediate filaments and microtubules, the other two main filament systems of the cytoskeleton, are rare or nonexistent in spines.

Actin filaments are extremely enriched in spines relative to other parts of the mature neuron

DENDRITIC SPINES

Protein	Concentration	Evidence
β-actin	Enriched	Light microscopy
γ-actin	Enriched	Light microscopy
α-actinin	Enriched	Light microscopy
α-adducin	Present	Electron microscopy
ADF	Present	Electron microscopy
Arp2/3 complex	Predicted	
Calcineurin	Present	Electron microscopy
Calmodulin	Present	Electron microscopy
Calpain	Present	Electron microscopy
CaMKII	Present	Light microscopy
Capping protein	Predicted	
Cofilin	Predicted	
Drebrin	Enriched	Electron microscopy
Ena/VASP family members	Predicted	
Fyn	Present	Subcellular fractionation
Gelsolin	Predicted	
α internexin	Present	Electron microscopy
Myosin IIB	Present	Light microscopy
NAP22	Present	Electron microscopy
NF-L subunit of neurofilament	Present	Subcellular fractionation
PKA	Present	Subcellular fractionation
PKC-γ	Present	Electron microscopy
Profilin	Predicted	
PP1 α	Enriched	Electron microscopy
PP1 γ1	Enriched	Electron microscopy
RC3/neurogranin	Present	Electron microscopy
Synaptopodin	Enriched	Electron microscopy
Spectrin	Present	Light microscopy
Spinophilin/neurabin II	Enriched	Electron microscopy
Tropomodulin	Predicted	
Tropomyosin	Predicted	
WASP family members	Predicted	

DENDRITIC SPINES



Spines contain two distinct pools of actin filaments (one stable, the other unstable) that provide the spine with both a stable core structure and a dynamic, complex shape

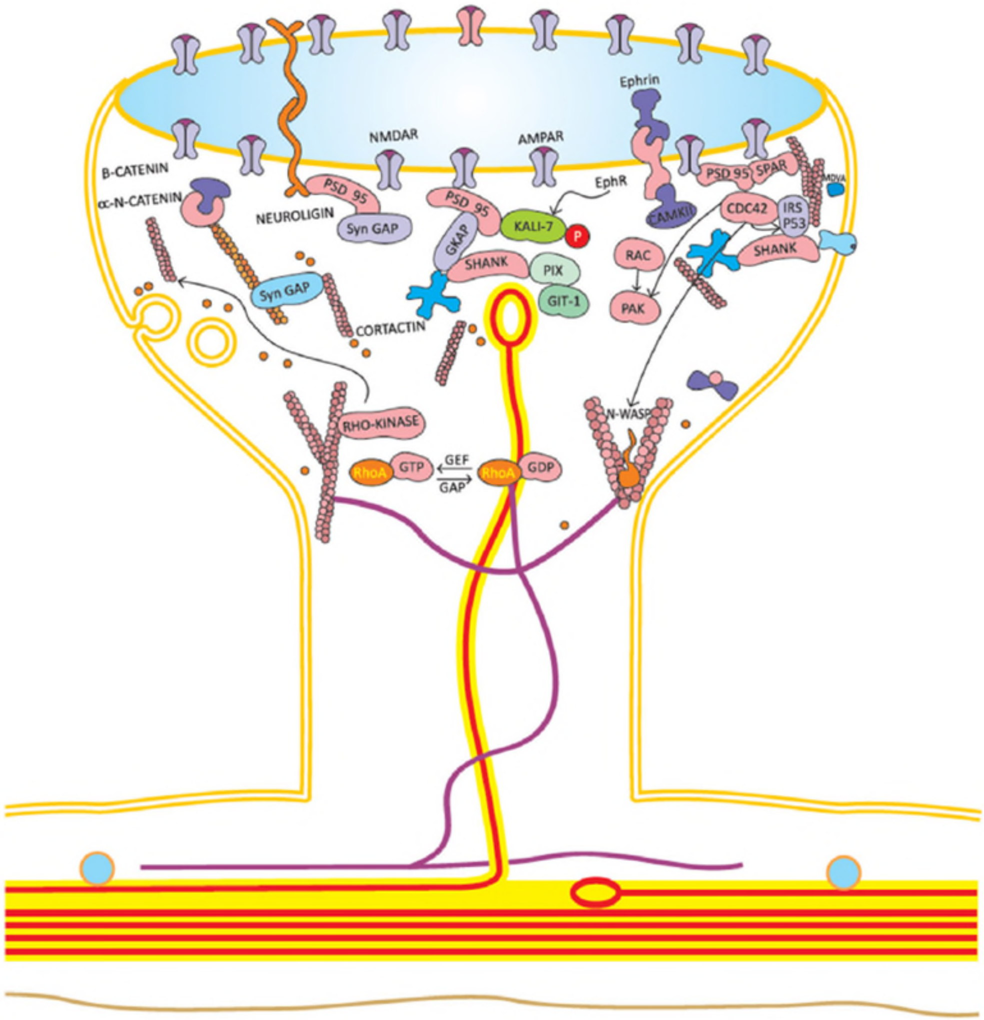


Fig. 2. Major components of dendritic spines. Synaptic activation (via AMPA and NMDA receptors by glutamate) alters structural molecule like PSD-95 which in turn stimulates RhoGTPases, or protein kinases signals. RhoA, Rnd1, Rac1 and Cdc42 are main regulators of dendritic spine morphology and synapse strengths.

Chidambaram et al., 2019

Signalling cascade that regulates spine shape and motility

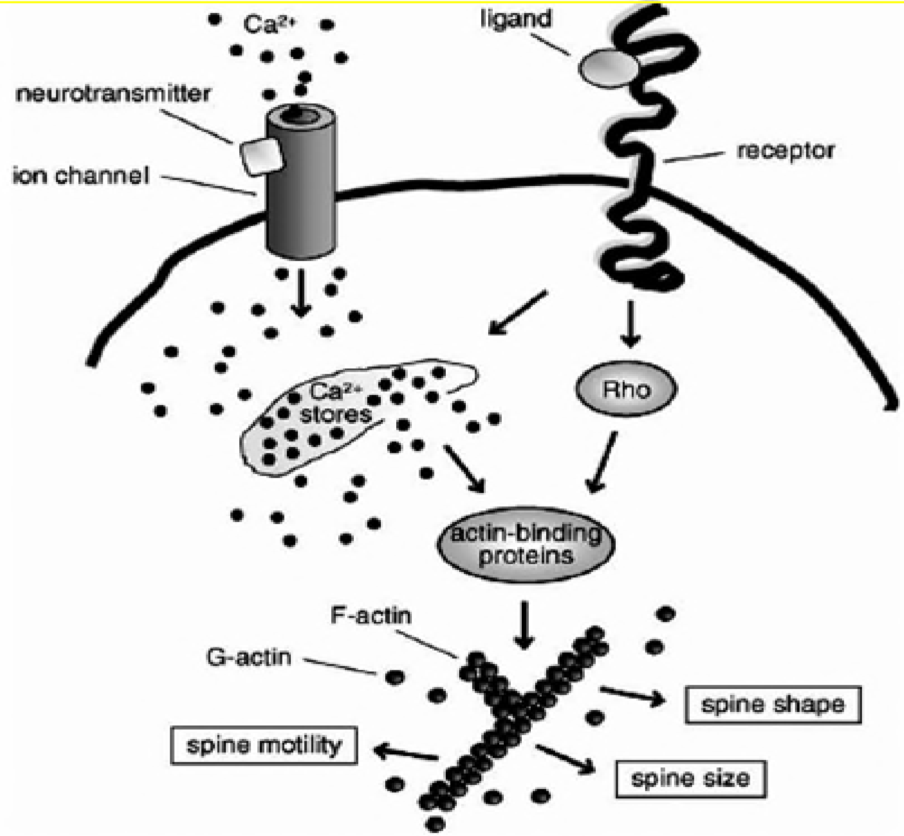
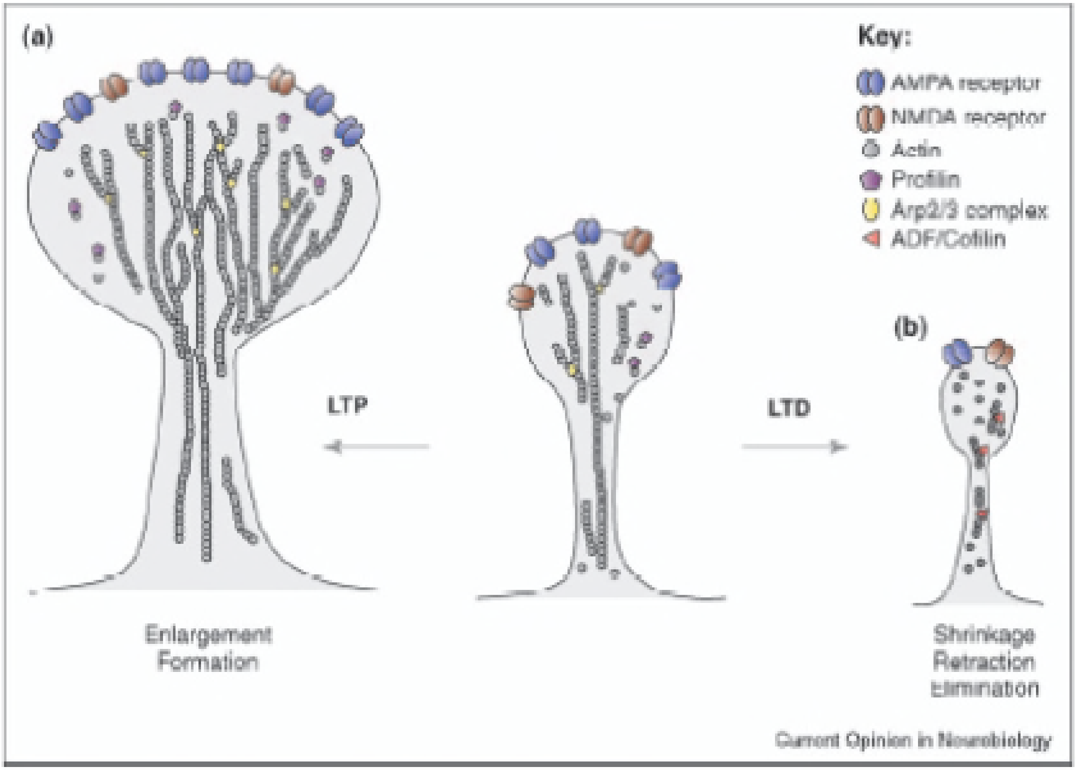


Fig. 3. The signaling cascades that regulate dendritic spine shape and motility involve cell surface receptors and ion channels, which activate signaling cascades controlling the activity of Rho GTPases and the Ca^{2+} concentration within the spine. Ca^{2+} permeable ion channels include neurotransmitter-gated ion channels, as shown, and voltage-gated Ca^{2+} channels (not shown). Cell surface receptors include receptor tyrosine kinases and cell adhesion and recognition molecules. These receptors can bind soluble ligands, as shown, or ligands anchored to adjacent cell surfaces or to the extracellular matrix (not shown).

I.M. Ethell, E.B. Pasquale / Progress in Neurobiology 75 (2005) 161–205

Changes in actin polymerization with LTP and LTD leads to changes in spine shape



Changes in actin polymerization and spine morphology with LTP and LTD. **(a)** LTP is associated with a shift of actin equilibrium toward F-actin (F-actin is depicted as linear chains of monomeric G-actin [single circle]) in spines, enlargement of the spine head, and recruitment of more AMPA receptors to the postsynaptic membrane. Profilin promotes actin filament assembly by increasing the availability of actin-ATP for polymerization. The Arp2/3 complex stimulates nucleation of new actin filaments and formation of branches. **(b)** By contrast, LTD stimulation shifts the equilibrium toward actin depolymerization, resulting in shrinkage or loss of spines. The actin severing protein ADF/cofilin might be involved in spine shrinkage.

Tada & Sheng. Current Opinion in Neurobiology 2006, 16:95–101

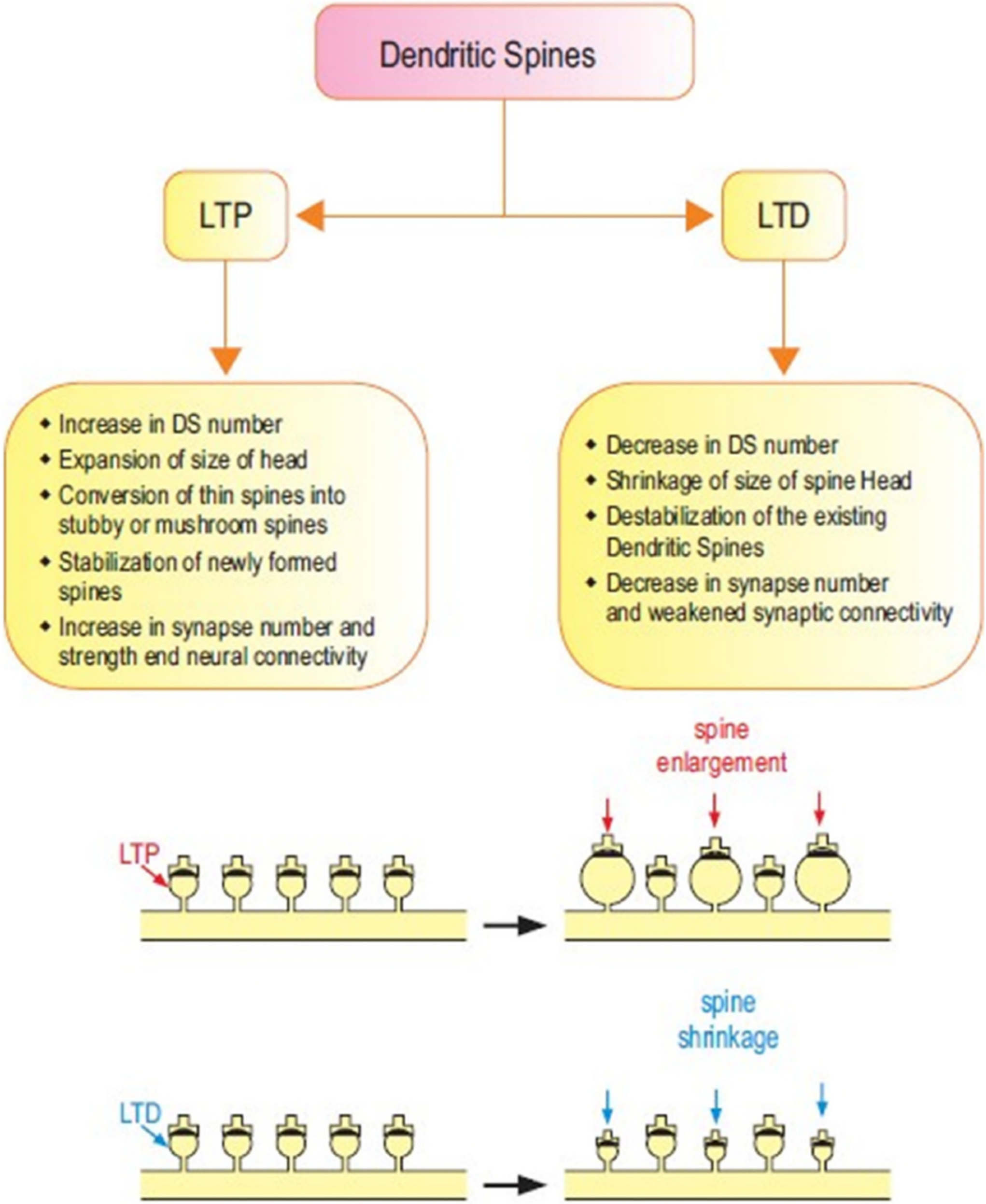


Fig. 7. Structural changes in a dendritic spine (a) repetitive LTP induction (via activation of AMPA and NMDA receptors) causes enlargement of spine head. (b) repetitive LTD induction causes spine head shrinkage (due to actin depolarization)

SUMMARY 1

Dendritic spines undergo several types of transformations, ranging from growth to collapse, and from elongation to shortening, and they experience dynamic morphological activity on a rapid time scale.

Changes in spine number and morphology occur under pathological conditions like excitotoxicity, but also during normal central nervous system development, during hormonal fluctuations, and in response to neural activity under physiological circumstances.

PROPOSED FUNCTIONS OF SPINES

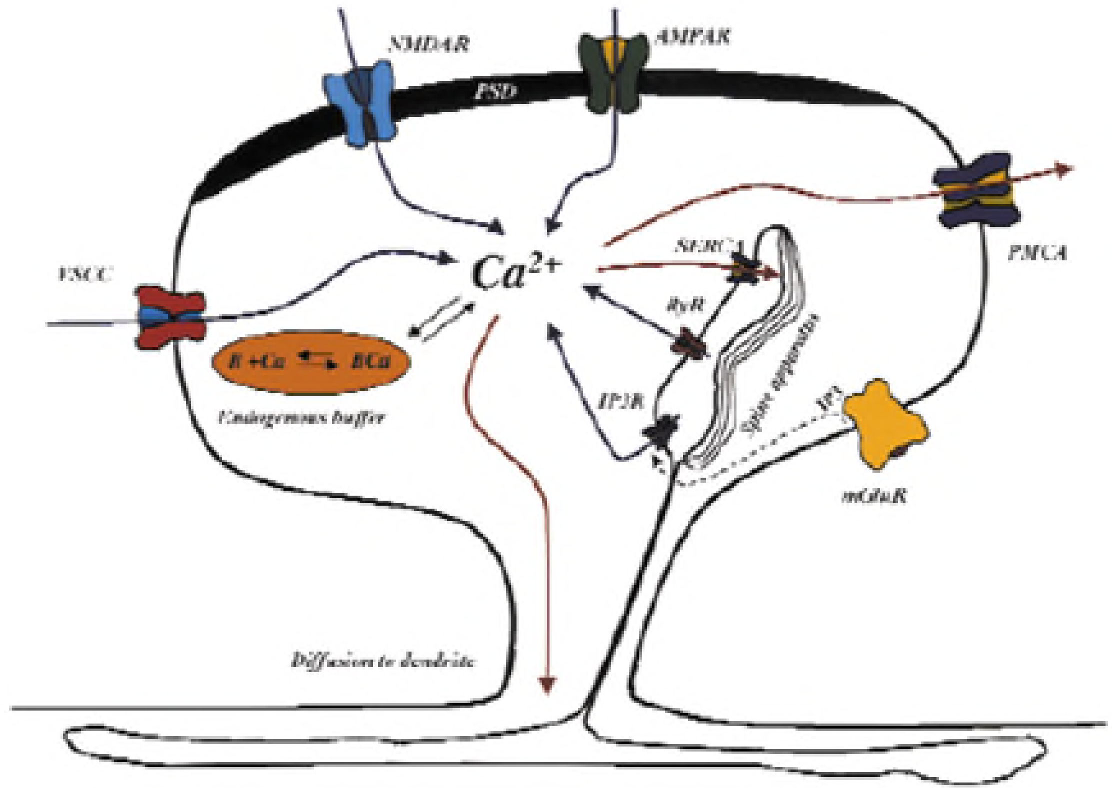
Dendritic spines are targets of most excitatory inputs in the central nervous system (CNS) and are morphologically heterogeneous

The spine is suggested to act as a biochemical compartment which isolates subsynaptic activity-driven calcium ion flux from the rest of the dendrite and therefore also from other nearby synapses .

The restriction of the calcium pulse to the spine is believed to allow localized signaling cascades, which act on spine constituents to induce local modifications of spine structure and composition.

Ca2+ entry in dendritic spines

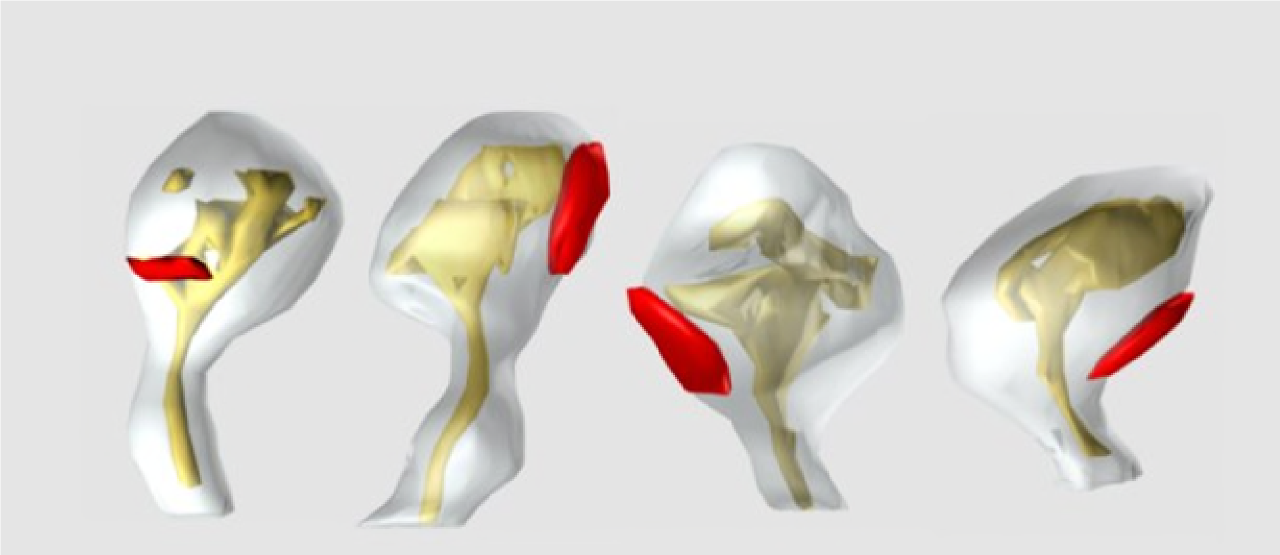
Fig. 4. Model of a spine. Cartoon illustrating the rich diversity of mechanisms that control calcium kinetics in spines. Blue arrows depict the influx of calcium into the spine; red arrows show calcium efflux. Influx can occur through NMDA channels, voltage-sensitive calcium channels (VSCCs) and calcium-permeable AMPA receptors. Calcium can also enter the cytoplasm from internal stores through a ryanodine receptor-dependent mechanism or through an IP_3R after activation of metabotropic glutamate receptors. In the cytoplasm, calcium can bind to calcium buffers (orange, B) whose kinetics and affinities alter the shape of the calcium transient. Calcium then leaves the spine by extrusion mechanisms such as the plasma membrane calcium ATPase (PMCA), which pumps calcium into the extracellular space, or the SERCA pump, which sequesters calcium into intracellular stores. Calcium can also dissipate by diffusing through the thin spine neck into the adjacent dendrite.



Ca2+ entering through NMDA receptor channels could initiate a feedback loop in which actin-driven changes in spine shape influence the efficacy of transmission at individual synapses.

Calcium-sensitive interactions between the actin-binding protein *a*-actinin

Ca2+ stores in dendritic spines

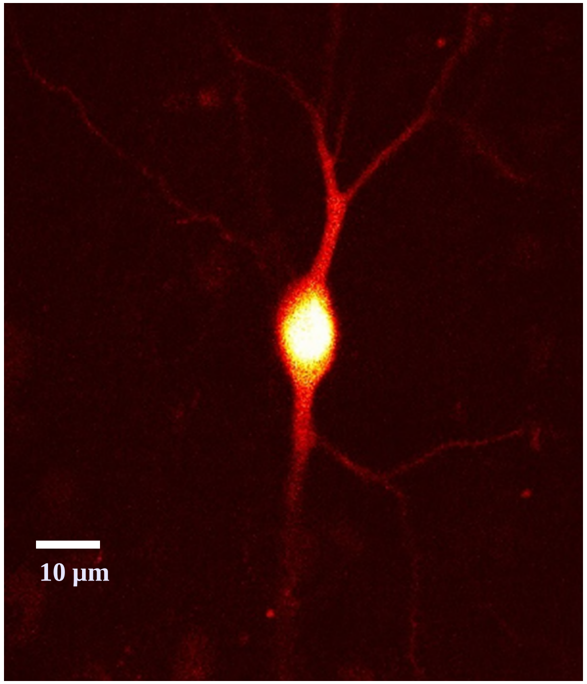


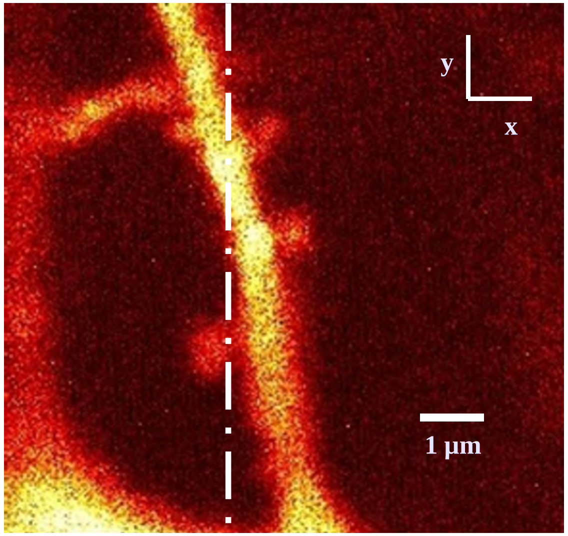
Synapse Web, Kristen M. Harris, PI

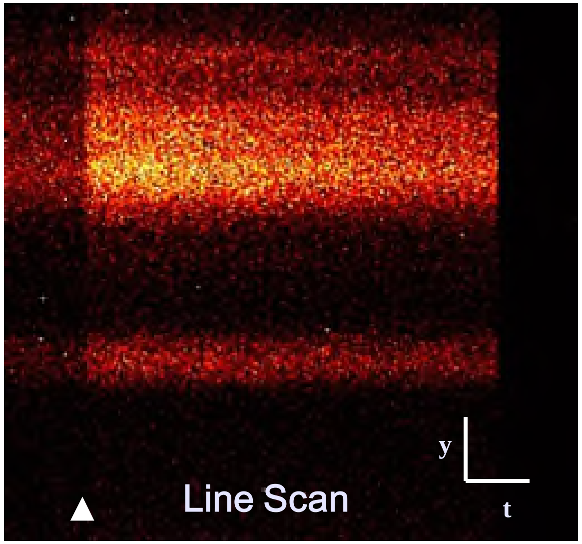
Dendritic spines are rich in smooth endoplasmic reticulum (known as the spine apparatus). This is found in mushroom spines of hippocampus, neocortex and cerebellum.

The spine apparatus plays a major role as Ca2+ store in spines

Confocal Laser Scanning Microscopy of CA1 hippocampal dendritic spines in rat organotypic slices



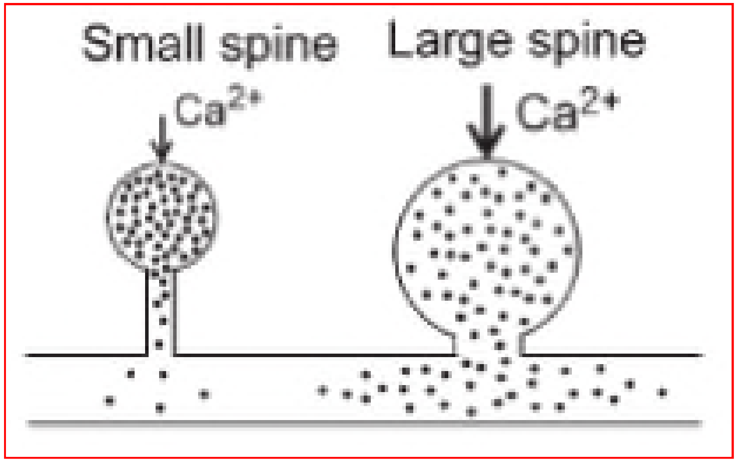




Pablo d'Alcantara, PhD
Department of Neurophysiology
National Institute for Medical Research
London, United Kingdom

Spine necks regulate biochemical and electrical signals in large and small spines

Calcium influx into spines is mediated by calcium channels and by NMDA and AMPA receptors and is followed by fast diffusional equilibration within the spine head

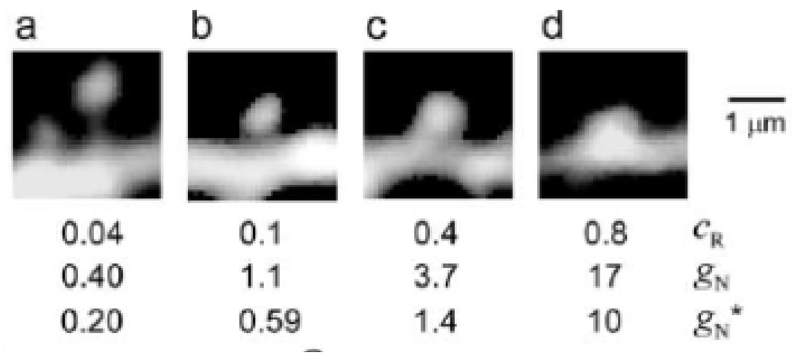


Compartmentalization of Ca2+ within the spine head is controlled by spine neck dimensions in both mushroom and thin spines of CA1 pyramidal cells: spines that have narrower or longer necks appear to retain more Ca2+ in their heads following synaptic activation than do wider shorter spines.

Relation between spine type and Ca2+

- Long and thin spines (type-III) spines may isolate Ca2+ transients from the parent dendrite and other spines

Low diffusion in dendritic shaft



High diffusion in dendritic shaft

- Shorter and stubbier spines (type-I) are thought to promote more coordinated and widespread Ca2+ transients in the parent dendrite, as well as to coordinate Ca2+ signalling among adjacent spines,

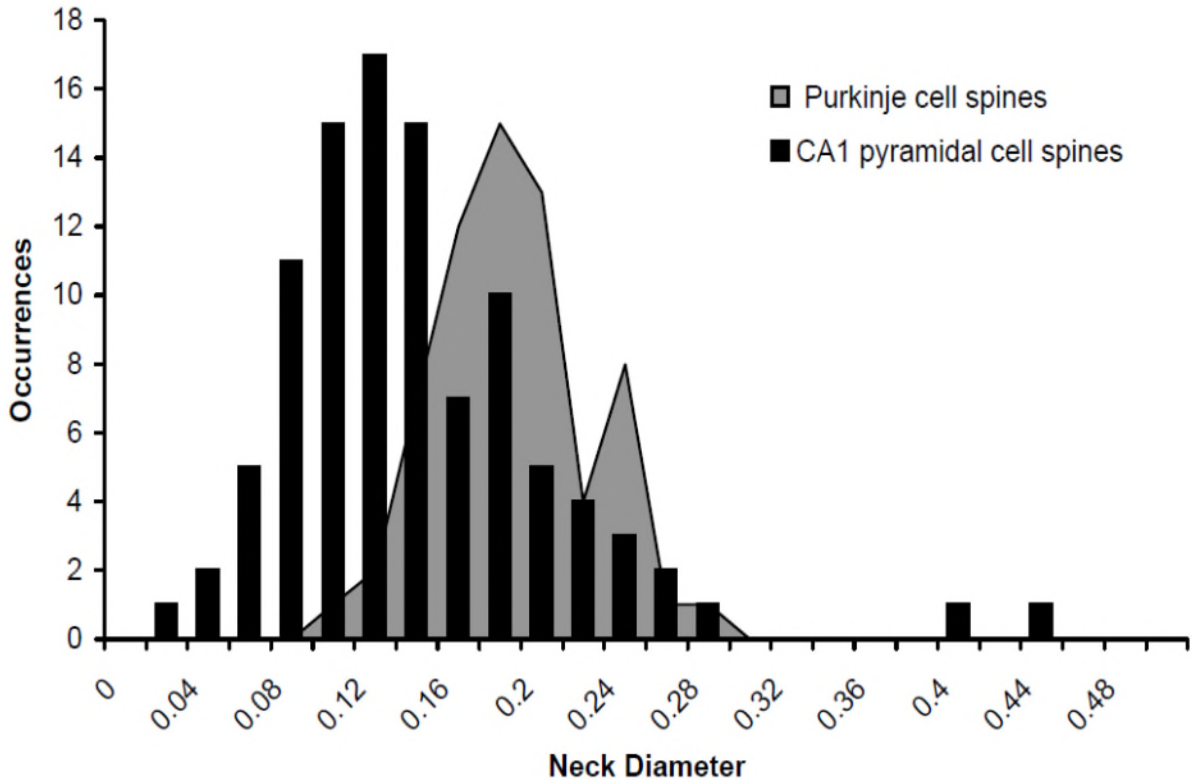


Fig. 1.9 The distribution of simple spine shapes as determined by three-dimensional reconstruction. a. Spines with a thin shape are most frequent in stratum radiatum of area CA1. These spines tend to have macular synapses (see text), the most common synapse shape. b. Measured neck diameters show a skewed distribution, with CA1 pyramidal cell spine necks tending to be thinner than those of spines from cerebellar Purkinje cell tertiary dendrites.

Dendritic spines: a note on disease

Certain neurological and neuropsychiatric diseases are associated with alterations in dendritic spines.

The density and morphology of spines is abnormal in many types of mental retardation

In fragile X syndrome and Patau's syndrome, the spines have been described as long and tortuous

Down's syndrome the neurons are either completely depleted of spines or are covered with innumerable small spines with almost invisible pedicle

Dendritic spines: neurodevelopmental disorders

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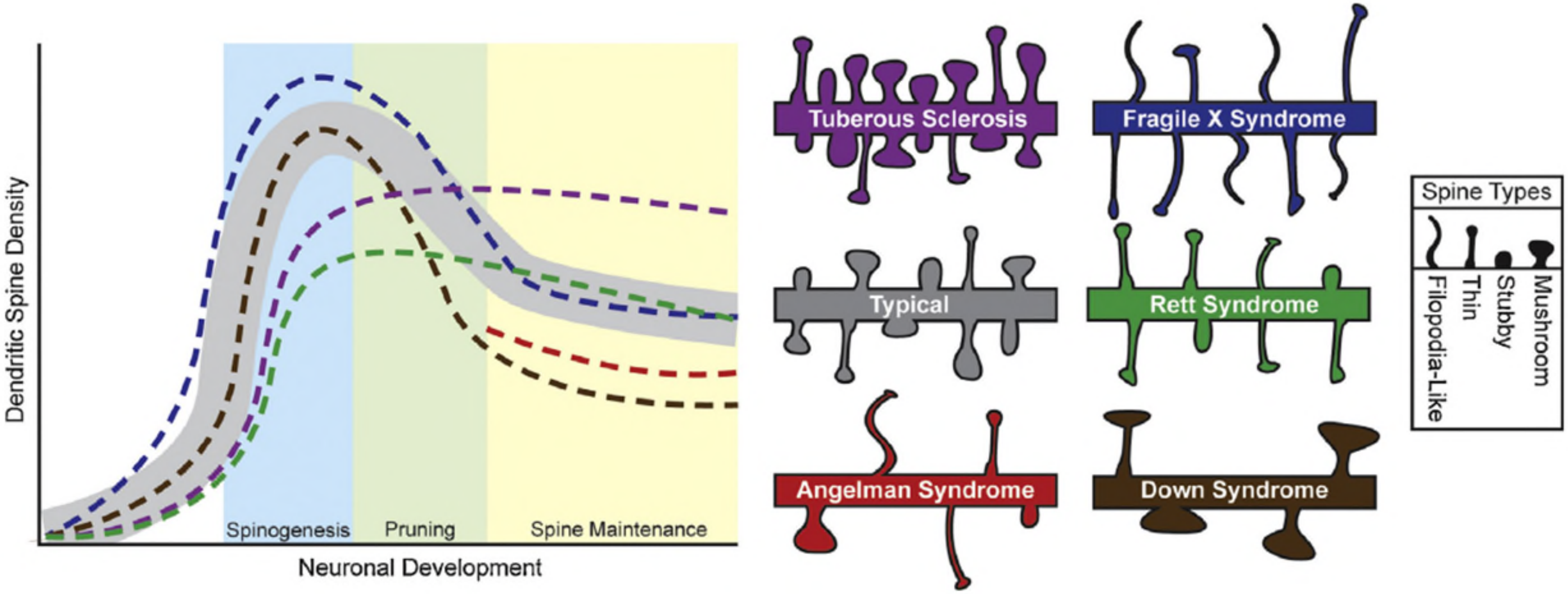

Fig. 1. Characterization of dendritic spines in autism related disorders.

SUMMARY

Dendritic spines are biochemical microcompartments that are isolated from their parent dendrites and neighboring spines. Spines compartmentalize Ca2+ and perhaps other messengers, such as IP3 and Na+ .

Imaging studies of spine [Ca2+] dynamics have revealed that Ca2+ can enters spines through voltage-sensitive and ligand-activated channels, as well as through Ca2+ release from intracellular stores.

In thin spines Ca2+ is more strictly compartmentalized

In large, short stubby spines Ca2+ is less strictly compartmentalized and can diffuse more easily in the parental dendrite