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Brain Research Reviews 39 (2002) 29–54

BRAIN RESEARCH REVIEWS

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Review

# Dendritic Spine Pathology: Cause or Consequence of Neurological Disorders?

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Accepted 14 March 2002

**Abstract**

Altered dendritic spines are characteristic of traumatized or diseased brain. Two general categories of spine pathology can be distinguished: pathologies of distribution and pathologies of ultrastructure. Pathologies of spine distribution affect many spines along the dendrites of a neuron and include altered spine numbers, distorted spine shapes, and abnormal loci of spine origin on the neuron. Pathologies of spine ultrastructure involve distortion of subcellular organelles within dendritic spines. Spine distributions are altered on mature neurons following traumatic lesions, and in progressive neurodegeneration involving substantial neuronal loss such as in Alzheimer's disease and in Creutzfeldt–Jakob disease. Similarly, spine distributions are altered in the developing brain following malnutrition, alcohol or toxin exposure, infection, and in a large number of genetic disorders that result in mental retardation, such as Down's and fragile-X syndromes. An important question is whether altered dendritic spines are the intrinsic cause of the accompanying neurological disturbances. The data suggest that many categories of spine pathology may result not from intrinsic pathologies of the spiny neurons, but from a compensatory response of these neurons to the loss of excitatory input to dendritic spines. More detailed studies are needed to determine the cause of spine pathology in most disorders and relationship between spine pathology and cognitive deficits.


*Theme:* Disorders of the nervous system

*Topic:* Developmental disorders; Epilepsy: human studies and animal models; Degenerative disease: Alzheimer's—other; Degenerative disease: Parkinson's; Degenerative disease: other; Ischemia; Trauma; Infectious diseases; Neuropsychiatric diseases; Neurotoxicity

*Keywords:* Dendrite; Dendritic spine; Synapse; Cerebral cortex; Cerebellar cortex; Mental retardation

## Contents



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0165-0173/02/$ – see front matter 
PII: S0165-0173(02)00158-3

## 1. Introduction

The principal neurons of most brain regions are covered with small protrusions known as dendritic spines. Dendritic spines are the main sites of excitatory synaptic input for these neurons. Dendritic spine distribution and structure is altered in many diseases, including various forms of mental retardation. The similarity of spine pathology in many different diseases lead to the recent proposal that many types of mental retardation result from an common inability of spiny neurons to form normal spines [137]. A more generally applicable alternative may be that spine pathology is symptomatic of a loss of connectivity rather than a cause of it. To investigate these issues we review the common characteristics and causes of spine abnormalities in a large number of pathological conditions.

The pathology of dendritic spines is of general interest for several reasons. Spines appear to serve several different functions [113,244], and observation of spine changes under the extreme conditions brought on by disease, injury, or experiment can help in understanding the relative importance of these functions. As principal sites of synaptic input spines play a key role in connectivity in the brain. Alterations in spine morphology that accompany disease are expected to have a significant impact on mental function. In addition, understanding spine plasticity in the extreme of pathological conditions will help elucidate the limits of normal synaptic plasticity during development, and during learning and memory in the mature brain.

Dendritic spines have received intense study in pathology because they are one of the few indicators of neuronal connectivity that can be seen with ordinary light microscopy [102]. However, only conditions far from normal physiological limits, that have dramatic effects on spine distribution, can be clearly identified in light microscopy. Likewise, only serious diseases resulting in deterioration of central nervous tissue, such as severe malnutrition or brain edema, generate sufficiently large changes in spine structure to be readily observed in conventional electron microscopy. Less extreme conditions, such as learning, electrical stimulation, anesthesia, acute intoxication, and aging, may lead to more subtle changes that go undetected in routine light and electron microscopy. For this reason, we do not discuss in detail many of these conditions nor do we consider experimental manipulations such as overexpression of particular proteins or animal genetic constructs, except where these are closely related to human neuropathology. Dramatic effects observed with reasonable descriptive methods are emphasized.

This review begins with a brief summary of normal dendritic spine anatomy and development to provide a context for assessing abnormalities. Typical spine pathologies are then summarized, followed by a limited review of specific diseases or conditions in which spine pathologies are commonly observed. Some of these data have been previously reviewed [238,102,124,126,137,141].

## 2. Dendritic spine structure, function, and development

Dendritic protrusions exhibit a wide-variety of shapes. Fiala and Harris [83] identified nine classes of synaptic specializations that protrude from dendrites in the central

nervous system (CNS). These protrusions range from simple spines to complex, multi-lobed excrescences with many synapses. Simple dendritic spines are by far the most common protrusion type on principal neurons of the CNS, and have been the main focus of most pathology studies. This review will focus primarily on simple dendritic spines.

A simple dendritic spine usually consists of a bulbous head attached to the dendrite by a narrow stalk or neck (Fig. 1). However, spines can be short and stubby with no neck constriction, or long and thin with no head enlargement. Dendritic spines vary greatly in neck diameter, length, volume, and surface area. Spine volumes can vary over at least an order of magnitude along a short segment of dendrite. Large spines, (often called mushroom spines,) have heads up to 1.0 μm in diameter. Spine necks can be as narrow as 40–50 nm in some instances, though most necks are more than 100–200 nm in diameter. Simple dendritic spines in dense neuropil are usually less than 2 μm long. Longer spines are occasionally found when target axons are farther away from the dendrites, such as when spines wind their way into adjacent axon bundles in the reticular nucleus of the thalamus and in the gelatinous substance of the spinal cord dorsal horn [238].

### *2.1. Filopodia and spine development*

Dendrites do not start out covered with spines. Newly formed dendrites are devoid of synapses and spine-like protrusions. During the period of synaptogenesis, dynamic, finger-like protrusions begin to emerge from the dendrites (Fig. 2). These filopodia form nascent synapses at contacts with axons or axonal filopodia [82]. Synapses can be seen all along the length and at the base of filopodia, and a single filopodium can receive multiple synapses. Often there is a swelling or enlargement in the filopodium at the locus of a synapse. Thus, when synapses occur at the tip, a filopodium can exhibit a bulbous head. Such a filopodium is still distinguishable from a spine in that it is longer than 2 μm and is filled with a denser actin matrix.

The filopodium is highly motile, extending and retracting its entire length in 10 min [54]. Filopodia are longest during early development, when the neuropil is less dense. They can be 10 μm long in some cases. Even neurons that are nonspiny at maturity exhibit dendritic filopodia during developmental synaptogenesis [298]. Thus, filopodia appear to be intimately involved in the process of synaptogenesis. Filopodia may be involved in locating and recognizing appropriate axonal partners, and guiding them to the dendrite. Filopodia can retract completely to leave shaft synapses in some cases while retracting into more spine-like shapes in others [54,82].

As synaptogenesis proceeds, dendrites begin to exhibit normal looking spines. These may emerge from the shaft synapses or form from retracted filopodia. The early spines often still receive more than one synaptic contact. Spine density increases during the synaptogenic period. On the dendrites of CA1 pyramidal cells in stratum radiatum, for example, spine density doubles between postnatal day 15 and adulthood [112]. As the neuropil becomes densely packed with axonal boutons and dendritic spines, dendritic filopodia decrease in length and frequency, and are rarely seen in the mature brain.

The cytoskeleton of dendrites is supported by microtubules, but these structures are absent from filopodia and simple spines. Filopodia and spines have a denser cytoplasm than dendrites, characteristic of an actin matrix [86].

Fig. 1. A reconstructed segment of a spiny dendrite from a pyramidal neuron reconstructed from stratum radiatum of hippocampal area CA1 of the adult rat. Excitatory synapses (red) reside on the enlarged heads of dendritic spines, while a couple of inhibitory synapses (blue) reside on the dendrite shaft. Scale=1 μm.

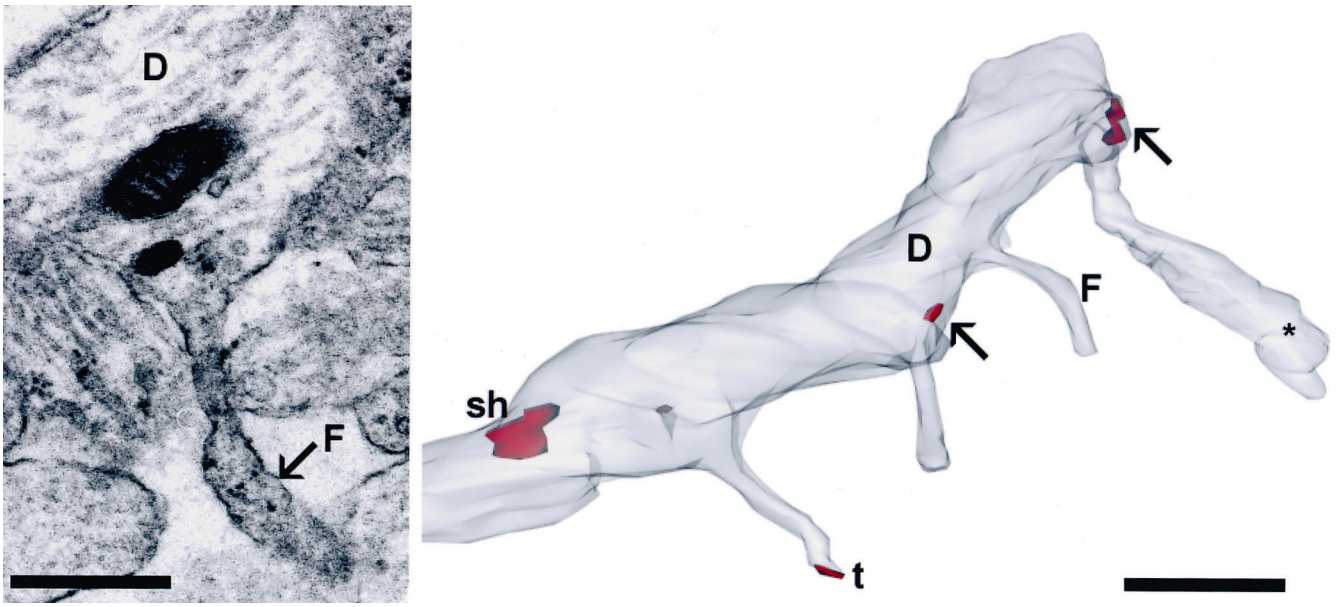



Fig. 2. Immature dendrites extend filopodia during synaptogenesis. Left: A filopodium (F) extending from a dendrite (D) in the hippocampus of a 4-day-old rat. The cytoplasm of the filopodium is darker than that of the dendrite, characteristic of a denser actin matrix. Scale=500 nm. Right: Reconstruction of a segment of this dendrite (D) reveals the 3D structure of this filopodium (F), and three additional filopodia. Synapses (red) occur at the base of filopodia (arrows), on the tip of a filopodium (t), or on the dendrite shaft (sh). One filopodium (asterisk), extending 3.4 μm from the dendrite shaft, is enlarged near the tip but receives no synapse there. Scale=1 μm.

This actin-based cytoskeleton is capable of supporting rapid changes in shape [177,304]. However spines seem relatively stable compared to filopodia, generally exhibiting rapid changes only in the shape of the spine head [88]. The overall motility of dendritic protrusions decreases with maturity [64]. Spines may be relatively immotile in the normal mature brain reflecting a stability of connectivity. Still, the latent motility of spines may allow rapid changes in spine density [110], and probably contributes to the high sensitivity of spines to pathological conditions.

### *2.2. Spine ultrastructure*

Little is known about the dynamics of dendritic spine organelles, since these are usually only observable with electron microscopy. Spines rarely contain mitochondria, but a variety of other organelles are observed. Many spines contain polyribosomes [256,261]. Some spines also contain endosomal vesicles involved in endocytosis and membrane recycling. Occasionally, an endosomal multivesicular body is found within larger spines [258]. Smooth endoplasmic reticulum (SER) also appears in some dendritic spines. The spines of cerebellar Purkinje cells nearly always contain SER [114], while only a fraction of spines contain SER in other brain regions [258]. SER cisternae within spines are continuous with the reticulum in the dendrite [174,256]. Larger spines contain larger amounts of SER that often is laminated in a characteristic structure called the *spine apparatus* [107,256].

Excitatory synapses on spines are readily identified in electron microscopy by the postsynaptic density (PSD), a densely staining region adjacent to the postsynaptic membrane. Dendritic spines in mature brain usually receive a single excitatory synapse on the spine head, but in some brain regions spines have a second synapse on the neck (e.g., Ref. [259]).

The size of the spine is closely related to the size of its excitatory synapse. Spine surface area, spine volume, bouton volume, and number of presynaptic vesicles are all highly correlated with synaptic area, while the length of the spine and the diameter of the neck are independent of synapse size [114–116,240]. The synaptic area is 10–17% of the surface area of the spine head [114,83]. Thus, large spines have large synapses. These large synapses are frequently perforated, with one or more nonsynaptic regions in the middle of the synapse [206,256].

### *2.3. Spine function*

Simple spines appear primarily in regions where the main excitatory axons are forming synapses in passing [238,267]. For example, the dendrites of cerebral pyramidal cells, granule cells of the dentate gyrus, and cerebellar Purkinje cells are densely covered with spines when mature. Over 95% of excitatory synapses on these neurons occur on the dendritic spines, with each spine head typically receiving one synapse [114,115,259]. The afferent axons pass perpendicularly through the dendritic arbors with vesicle-filled varicosities along their length. Most

(75%) of these *boutons en passant* make just one synaptic contact [245,247].

The density of spines on the dendrites is related to the degree of connectivity between these neurons and the axons that pass through their dendritic arbors. Consider that CA1 pyramidal neurons have three spines per μm of dendrite in stratum radiatum [112], while cerebellar Purkinje neurons have as many as 15 spines per μm [114]. The higher density reflects increased connectivity between Purkinje cells and the axons that pass through their dendritic arbors. In spinal cord, where synapses are just as densely packed as in cerebral cortex [180], the principal neurons receive most synapses directly onto dendrites rather than on spines. Here the axons are forming complex terminal arborizations rather than boutons en passant. The complexity of connectivity can thus be supported by the axonal branching rather than by dendritic spines.

There is no consensus on the purpose of dendritic spines, although it seems clear that connectivity is a central role [267]. Dendritic spines appear to serve other important functions as well [113,244]. Spines compartmentalize $Ca^{2+}$ and other signaling components, conferring specificity to changes in synaptic efficacy [52,187]. This compartmentalization of calcium in spines might also help protect the dendrite and neuron from excitotoxicity by restricting the high calcium concentrations to the region of the synapse [113,243]. In light of these multiple spine functions, pathological changes in spine number or structure will clearly have significant consequences for brain function.

## 3. Pathological changes in spines

Pathological changes in spines can be classified into two general categories, pathologies of distribution and pathologies of structure. Pathologies of distribution (Table 1) include dramatic increases and decreases in spine density, and widespread changes in morphology. Commonly observed morphological changes include an overall reduction in spine size or alteration in spine shape, dendritic beading with concomitant loss of spines, and sprouting of spines in abnormal locations. Pathologies of structure (Table 2) include all those changes observable in single spines, such as densification of the cytoplasm, hypertrophy of organelles or spine volume, and formation of aberrant synapse-like connections.

### *3.1. Decrease in spine density*

Many conditions lead to decreased numbers of dendritic spines (Table 1). Spine loss can be caused by the loss of the axons that normally synapse on spines. This type of spine loss occurs within a few days of deafferentation, and is often followed by reactive sprouting of other afferents with at least partial recovery of spine density. If these other afferent sources are also lesioned however, little recovery occurs [46]. Permanent spine loss is evident in most forms of mental retardation, including those resulting from prenatal infection, malnutrition and toxin exposure. Spine loss is also seen in epilepsy, prionoses and other neurodegenerative disorders. These conditions also have decreased numbers of neurons, suggesting that spines are lost as a result of a severe decline in the number and availability of axonal inputs to dendritic spines. In some progressive conditions, spine loss begins with axon degeneration before neuron loss can be detected [29,108]. In addition, it should be noted that spine loss can occur without loss of inputs. For example, the 30% decrease in spine density on apical dendrites of hippocampal area CA1 pyramidal cells during the estrus cycle [301] may involve gain and loss of spine synapses without gain and loss of axons in area CA1. Estradiol treatment in ovariectomized animals (Section 4.13) leads to increased spine density with a concomitant increase in multiple synapse boutons, suggesting that the new spines make synapses with existing axons [303].

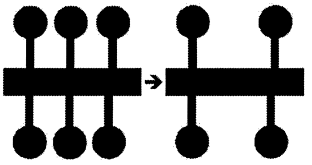
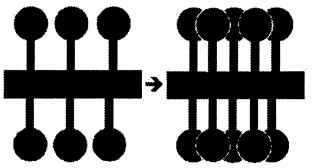
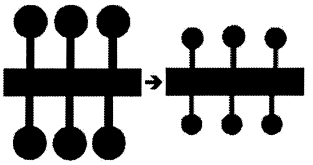
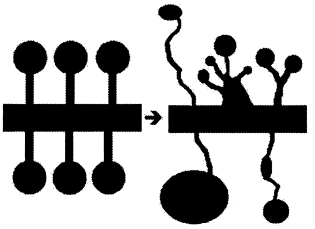
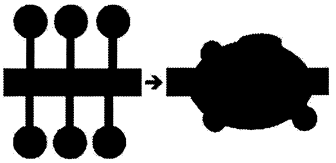
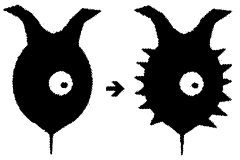
### *3.2. Increase in spine density*

An increase in spine density is a less common outcome of disease or injury, but it does occur (Table 1). In many brain regions, normal development involves an increase in synapses followed by pruning to mature levels [127]. Disruption of this developmental pruning may be a route to increased spine density. For example, ovariectomy disrupts pruning in visual cortex [189]. Similarly, an overabundance of dendritic spines in the reticular formation, vagal nuclei and ventrolateral medulla in infants dying from sudden infant death syndrome appears to represent a failure of developmental synapse elimination, and may be involved in the defective cardiorespiratory regulation [197,213,268–270]. Defective pruning has also been blamed for increased spine density seen in phenylketonuria [146] and fragile-X syndrome [130].

Environmental enrichment during development also results in increased spine and synapse density on pyramidal cells in occipital cortex [103,283] and in hippocampal area CA1 [27]. Interestingly, enrichment does not increase spine density in fetal alcohol syndrome [27]. This suggests that conditions leading to decreased spine density, such as fetal alcohol syndrome (Section 4.6), also block the potential for spine density increases.

In most cases the cause of a spine density increase is unknown, but several possibilities should be considered. The number of spines may increase when inputs that contribute to the suppression of synapses are lesioned, such as with climbing fiber lesions to cerebellar Purkinje neurons [79]. In other cases of deafferentation, dendritic atrophy may be so severe that the fewer remaining dendrites may express more spines to compensate for the

Table 1
Pathologies of spine distribution and shape

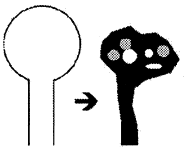
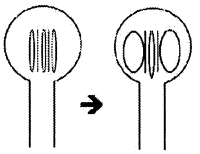
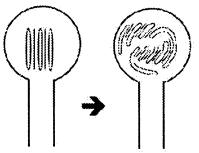
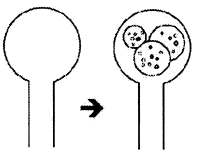
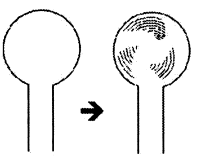
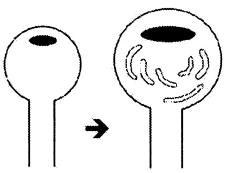
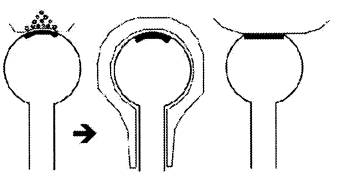
| Section | Spine Pathology | | Occurrence | Fig. |
|---|---|---|---|---|
| 3.1 | Decrease in spine density |  | deafferentation, agenesis, most mental retardation, malnutrition, poisoning, alcohol abuse, epilepsy, spongiform encephalitis, Alzheimer's disease, and others | 3 |
| 3.2 | Increase in spine density |  | some types of deafferentation, environmental enrichment, fragile-X syndrome, sudden infant death syndrome, stimulatory drug use | 3 |
| 3.3 | Reduction in spine size |  | sensory deprivation, schizophrenia, Down's syndrome | not shown |
| 3.4 | Distortion of spine shape |  | deafferentation, agenesis, malnutrition, epilepsy, most mental retardation, alcohol abuse, poisoning, spongiform encephalitis | 3 |
| 3.5 | Varicosity formation |  | acute excitotoxicity, traumatic injury and edema, epilepsy, hypoxia/ischemia | 3, 4 |
| 3.6 | Ectopic spines |  | olivopontocerebellar atrophy, Menkes disease, metabolic storage diseases | not shown |

overall loss of input [266]. While it is unclear that increased numbers of available axonal inputs leads to more spines in the same way that decreased afferents lead to spine loss, this too remains a possibility. For example, repeated use of stimulatory drugs can lead to increased spine density (Section 4.6), but it is not known whether this increased density involves increased numbers of axons.

### *3.3. Reduction in spine size*

As pointed out by Globus [102], the morphology of

Table 2
Pathologies of spine ultrastructure

| Section | Spine Pathology | | Occurrence | Fig. |
|---|---|---|---|---|
| 3.7 | Electron-dense spines |  | brain edema, traumatic injury, neurodegeneration | 5 |
| 3.8 | Altered endoplasmic reticulum |  | brain edema, intoxications | not shown |
| 3.8 | Hypertrophied spine apparatus |  | brain edema | 6 |
| 3.8 | Hypertrophied multivesicular bodies |  | brain edema | 10 |
| 3.8 | Hypertrophied cytoskeleton |  | brain edema | 10 |
| 3.9 | Giant spines |  | deafferentation, malnutrition | 7 |
| 3.10 | Axonless spines with axon-free postsynaptic density |  | deafferentation, agenesis | 8 |

dendritic spines is dependent not only on the structural integrity of the afferent axons but on their functional integrity as well. Experiments with visual deprivation by eyelid closure have reported mixed effects on spine density in visual cortex [85,105,163,284]. However a frequent finding with visual deprivation from birth is a reduction in synapse and spine size [93,105,277], and an absence of the normal complement of large, perforated synapses on spines [12,277]. Apparently spine volume is reduced in the absence of normal levels of presynaptic activity, while the number of spines stays relatively unchanged. However, sensory deprivation has also been shown to reduce the motility of dendritic protrusions during synaptogenesis in somatosensory cortex without reducing protrusion size or density [152].

A reduction in spine size along entire dendrites has been reported in the striatum of schizophrenics [223], and in motor cortex of Down's syndrome infants [169]. This suggests the possibility that in these conditions, as in deprivation, some dendrites may receive synapses from relatively quiescent axons.

### *3.4. Distortion of spine shape*

Principal neurons in many forms of mental retardation have dendrites with distorted spine shapes (Section 4.4). The spines are unusually long and tortuous, sometimes with multiple swellings or no head enlargement at all (Fig. 3). Deafferentation also produces such distorted spines (Section 4.1), suggesting that, in general, this spine pathology could be a response to loss of axons. Many aspects of this distorted spine morphology are similar to the early developmental state of neurons in which dendrites exhibit long filopodia, sometimes with multiple fusiform swellings (Section 2). Dendritic protrusions in early development can appear very much like the elongated spines in mental retardation [82]. Perhaps the lower density of axons in the vicinity of afflicted dendrites provokes compensatory mechanisms similar to those seen in development in which spines elongate and snake through the neuropil to reach axons farther away. These abnormal spines may be highly dynamic structures like filopodia, but spine motility in mental retardation, deafferentation, and other conditions has not yet been investigated.

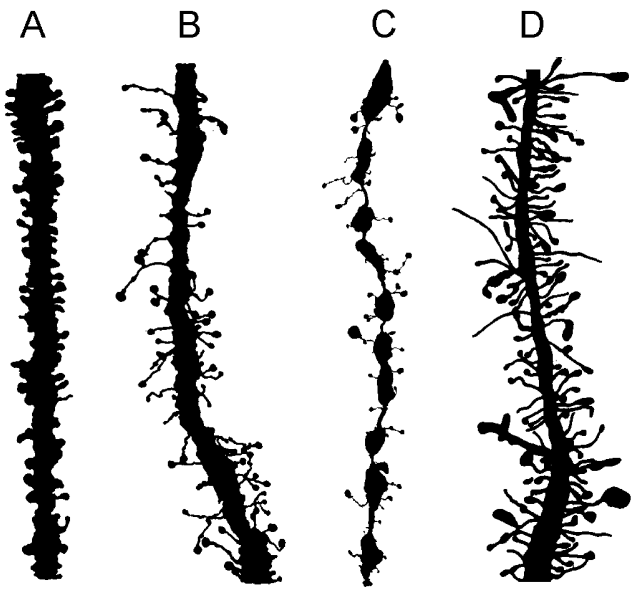



Fig. 3. Camera lucida drawings of apical dendrites of pyramidal cells from human cerebral cortex. A dendrite from normal 6-month-old infant with no history of neurological disorder (A) has a large number of spines, while an analogous dendrite from a retarded 10-month-old child (B) shows long, tortuous spines. (Reprinted with permission from Ref. [211]. Copyright 1974 American Association for the Advancement of Science). A dendrite from a 5.5-month-old child with severe neurobehavioral failure (C) shows numerous varicosities and long, thin spines. (Reprinted with permission from Ref. [212]. Copyright 1982 Elsevier Science). A dendrite from an adult case of fragile X syndrome (D) has a high density of elongated and enlarged spines. (Reprinted with permission from Ref. [297]. Copyright 1991 Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.).

### *3.5. Varicosity formation*

The formation of dendritic varicosities is often seen in response to brain or neuronal injury. Loss of isotonicity is accompanied by swelling of dendritic trunks, usually producing varicosities. The swelling of dendrites can be compared to the inflation of a surgical glove, the fingers of which disappear with the expansion of the ballooned surface. In the same way, dendritic spines are absorbed by the expansion of varicosities [218] (Fig. 4). Amazingly, spines absorbed in this manner can recover their original shape after termination of the insult and elimination of dendritic swelling [117]. Focal dendritic swelling with loss of spines occurs in edematous neuropil (Section 4.9), and in acute excitotoxicity caused by anoxia/ischemia [1,198], convulsive drug application [61], epilepsy [22,239], and postmortem degradation [218].

Dendrites in a number of progressive neurodegenerative disorders exhibit non-hydropic varicosities that may also be related to spine loss. These include Huntington's disease [252], frontal lobe dementia and motor neuron disease [80], as well as Alzheimer's, Pick's, and Creutzfeldt–Jakob disease [77,123]. These varicosities may contain abnormal intracellular inclusions associated with the disease, such as the Lewy bodies in Parkinson's disease varicosities [202,203]. Focal dendritic swellings with inclusions are seen in many other conditions as well, such as in mucopolysaccharidoses [73]. Purpura et al. [212] reported that varicosities associated with disordered spines were related to abnormal organization of dendritic microtubules in some cases of infantile neurobehavioral failure (see Fig. 3C).

### *3.6. Ectopic spines*

The appearance of spines in locations where they are not

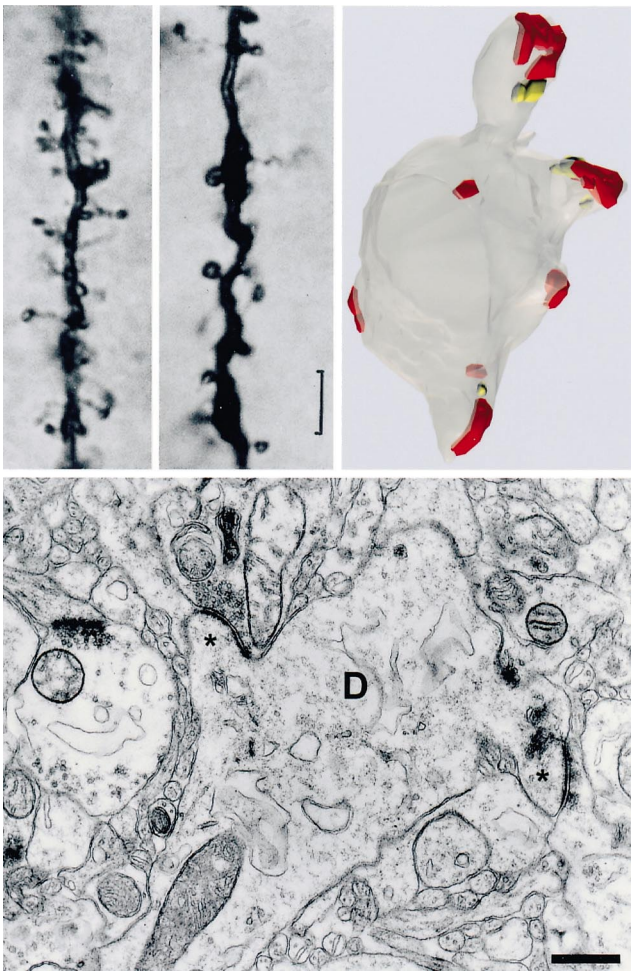



Fig. 4. Varicose swellings in human neocortex in the vicinity of a tumor give dendrites a beaded appearance and absorb spines when enlarging. Upper left: Light micrographs compare a control dendrite (left) to a dendrite with varicosities, spine loss and retracted or sessile spines (right). Scale=2 μm. (Reprinted with permission from Ref. [257]. Copyright 1987 Springer-Verlag). Upper right: Three-dimensional reconstruction of a varicosity showing loci of synapses (red) and puncta adherentia (yellow) on absorbed spines. Bottom: A hydropic dendrite (D) with two aberrant spines (asterisks) containing remnants of spine apparati. Scale= 500 nm.

normally found may indicate a persistent, or retroactive, developmental state. Like dendritic filopodia (Section 2.1), somatic protrusions are found on some neurons only during early development [149]. Somatic spines appear on Purkinje neurons at abnormally later times in disorders such as olivopontocerebellar atrophy [79], fetal alcohol syndrome [184], Menkes disease [121], hypothyroidism [151], and transmissible spongiform encephalopathy [20]. Somatic spines are also seen in the adult rat dentate gyrus immediately after slice preparation [295].

Other causes of ectopic spines include abnormal patterns of innervation and metabolic storage disorders. Axonal sprouting in reaction to experimental epilepsy leads to abnormal dendritic spines on dentate granule cells [222]. In addition, granule cell somatic spines can appear within 3 h of the initiation of seizures [31,32]. Ectopic dendrites and spines sprout from the axon hillock in gangliosidosis [290] and sphingomyelin lipidosis [289]. Clearly, there are diverse causes of ectopic spines, but some instances of ectopic protrusions may indicate compensatory synaptogenesis in response to a loss of axosomatic input.

### *3.7. Electron-dense spines*

Damage to a neuron often leads to changes in dendritic hydration, either increased or decreased, with notable structural impact on spines. In addition to the hydropic swelling already mentioned, neurons can exhibit a densification of cytoplasm followed by a loss of organelle integrity. Electron-dense spines appear dark when observed by transmission electron microscopy. They are a product of degenerating dendrites (Fig. 5), often associated with dying cells (e.g., Ref. [156]). Electron-dense spines are common in regions of necrosis, such as with traumatic injury (Section 4.9), but can also be found in other neurodegenerative conditions such as Alzheimer's disease [14] and in convulsant-induced degeneration [65].

### *3.8. Alterations of spine organelles*

Spine pathology may also involve alterations in spine organelles (Table 2), although this has been studied to a much lesser extent in disease than changes in spine distribution. Alterations in spine organelles result from diverse causes. In some cases this involves injury to the postsynaptic cell. In other cases excitotoxic injury from excessive presynaptic glutamate release may be the principal factor. Pathological changes have been reported in the synapse and postsynaptic density, polyribosomes, endosomes and the spine cytoskeleton. The postsynaptic density is thickened by anoxia/ischemia [173]. A higher density of polyribosomes has also been observed in spines after deafferentation [260]. Changes in spine endosomes and cytoskeleton have been occasionally observed in edema (Section 4.9).

An organelle found in many spines that has accordingly received a lot of attention is the smooth endoplasmic reticulum and spine apparatus. Pathology frequently seen in edematous tissue is hydropic swelling and vacuolization of the endoplasmic reticulum of dendrites and spines [38,257]. This type of dilation is also seen in Purkinje neuron spines with chronic ethanol abuse [62]. In addition to swelling, the spine apparatus can become elaborated (Fig. 6), or atrophied [38]. A reduction in spine apparatuses has also been reported in anesthetized animals [60]. Interestingly, one ataxic rat mutant shows a complete absence of smooth endoplasmic reticulum in spines of Purkinje cells [56].

### *3.9. Giant spines*

Neurons appear to have a number of allostatic mechanisms for maintaining excitatory drive at an appropriate

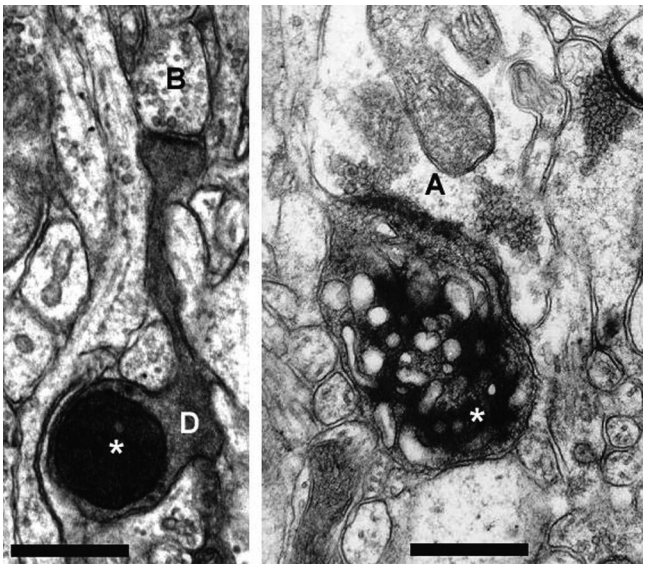



Fig. 5. Electron-dense dendritic spines. Left: A dendrite (D) from a rat hippocampal slice has a dense cytoplasm and an enlarged mitochondrion (asterisk). A dark spine synapsing with a normal looking bouton (B) extends from the degenerating dendrite. Scale=500 nm. Right: A hydropic axon terminal (A) synapses on an electron-dense and vacuolated spine (asterisk) in human peritumorous cortex. Scale=400 nm.

level. One mechanism to recover excitatory drive is to increase the number of excitatory synapses [143]. However, when few axons are available for additional input, giant spines may result. Giant spines (Fig. 7) form in response to deafferentation as an apparent compensatory mechanism for decreased numbers of presynaptic axons. Enlarged synapses made with the few remaining axons may represent an attempt to recover excitatory drive. Since spine volume is directly related to synapse size in normal brain (Section 2.2), the occurrence of giant synapses on giant spines suggests that postsynaptic mechanisms are operating normally to maintain this relationship. In this sense, giant spines represent an exaggerated morphological equivalent of synaptic scaling to compensate for lost input [281,282].

### *3.10. Axonless spines*

Although frequent during development, dendritic protrusions lacking axonal synaptic partners are rare on spiny neurons in the mature brain. Axonless spines can be occasionally found in normal brain [214,255]. These spines exhibit a PSD-like structure apposed to a structure other than an axon. In cortex, these axon-free PSDs may be apposed to specialized subsurface cisternae of SER in perikarya (Fig. 8).

The frequency of axonless spines is increased when a spiny neuron is deafferented by lesion [13,43,45,214], or by neurodegenerative disease [148]. These axonless spines often exhibit axon-free PSDs at synapse-like junctions with glia or other dendrites. However, the presence of an axon-free PSD depends on the availability of an aberrant junctional partner, such as a glia process. Only spines adjacent to such partners exhibit axon-free PSD junctions in culture [13]. Although the increase in axonless spines following deafferentation is transient in the mature brain, in developmental agenesis of cerebellar granule cells, Purkinje cell dendrites continue to exhibit axonless spines well into maturity [5,215,248]. It is not known whether individual axonless spines are transient, with rapid turnover like filopodia, or whether they are relatively stable and permanent like normal spines. The appearance of stability is often convincing, such as when Purkinje cell spines make synapses with the dendrites of Golgi neurons that contain presynaptic vesicles [249].

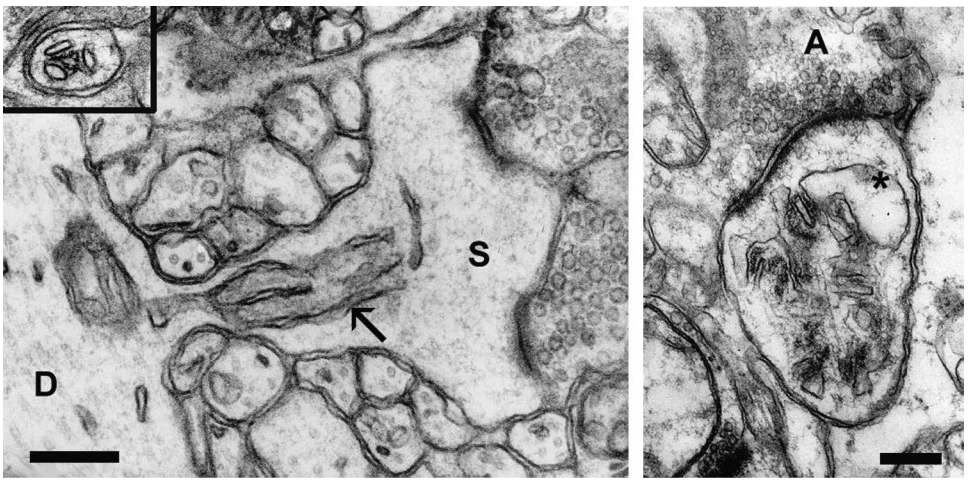



Fig. 6. The appearance of the spine apparatus in normal and diseased brain. Left: A large spine (S) extending from a dendrite (D) contains a spine apparatus (arrow) in the spine neck. Scale=300 nm. A spine neck containing a spine apparatus cut transversely is shown in the inset. (Hippocampus, rat). Right: A dendritic spine from human peritumorous neocortex synapses with a normal looking axon terminal (A). The spine is filled with a hypertrophic spine apparatus, one of the cisternae of which is dilated (asterisk). Scale=200 nm.

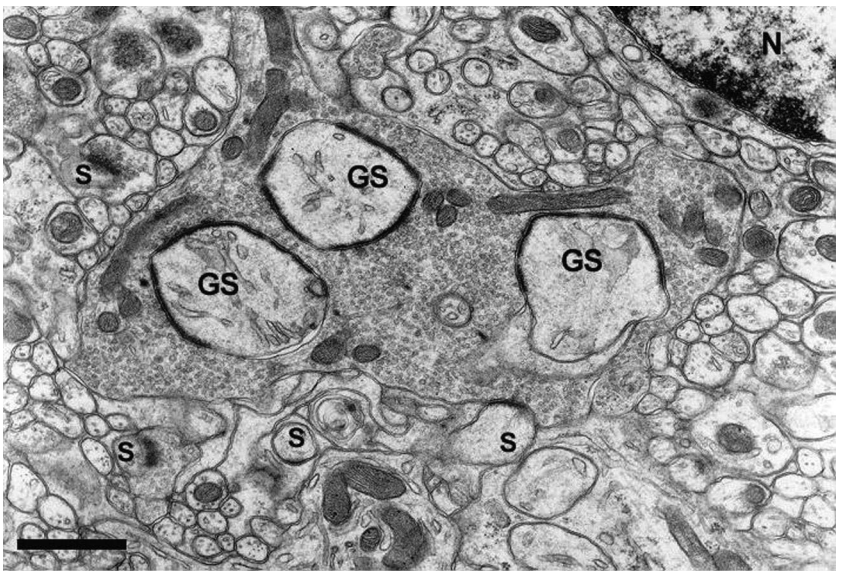



Fig. 7. Purkinje cell giant dendritic spines invaginate a large axon terminal. Compare the sizes of giant Purkinje cell spines (GS) and the enlargement of their synapses with those of regular spines (s). A neuronal nucleus (N) is nearby. This occasional finding from the molecular layer of mouse cerebellar cortex fully corresponds in appearance with giant spines described as a result of proteinaceous undernutrition. Scale=500 nm.

## 4. Conditions leading to spine pathology

A variety of insults and diseases can lead to the same characteristic spine pathology. While the following review is far from exhaustive, it provides additional perspective on the possible role of axon loss as a general cause of many different spine pathologies. The review focuses on findings of the last 2 decades. The study of spine pathology has a long history as can be appreciated from older reviews [102,238].

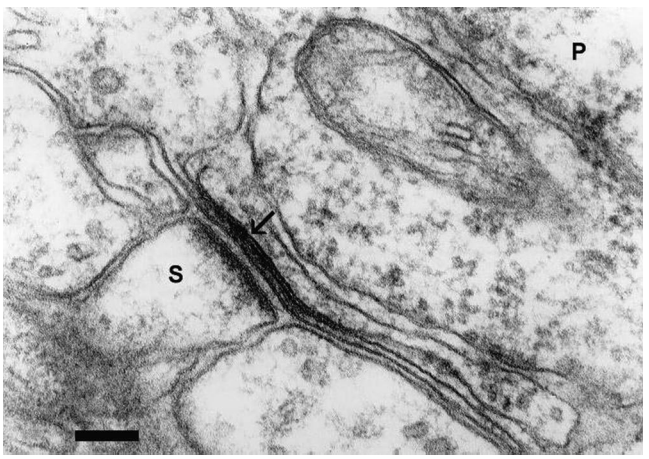



Fig. 8. This dendritic spine (s) containing a postsynaptic density is not accompanied by a presynaptic terminal axon (axon-free postsynaptic density). Instead, it is associated with the perikaryal plasma membrane and a subsurface cistern (arrow) of a nerve cell (P). (Normal rat thalamus). Scale=200 nm. (Reprinted with permission from Ref. [255]. Copyright 1982 Kluwer Academic Publishers).

### *4.1. Adult deafferentation and lesions*

The effect of deafferentation by lesion of afferent pathways has been intensively studied in animals, where the consequences of experimental manipulations can be readily observed. The majority of deafferentation studies show dendrite atrophy and spine loss [102]. The acute pathology begins with degeneration of the distal pieces of the severed axons and their synaptic boutons (Fig. 9). This anterograde degeneration of boutons is sometimes referred to as Wallerian degeneration [219]. As degenerating boutons are removed, many spines and their synapses are lost within a few days [176,214]. This loss occurs, for example, in pyramidal cells after undercutting cerebral cortex [230], in granule cells of the dentate gyrus following lesions of entorhinal cortex [199,262], in cerebellar Purkinje cells after transection of parallel fibers [42,186], and in striatal spiny neurons after lesioning cortical afferents [46].

Deafferentation can be followed by reactive mechanisms that restore the lost synaptic complement, albeit from abnormal afferent sources. In septal nuclei [214], striatum [46], and dentate gyrus [182,199,262], where sprouting axons reinnervate the neurons, synaptic recovery can be substantial. The degree of recovery depends, obviously, on the extent of deafferentation and the ability of remaining axons to proliferate. In most regions the density of dendritic spines does not fully recover even months after deafferentation [285]. An additional compensatory mechanism is often seen in which much larger synapses are formed with the few remaining synaptic boutons [43,44]. For example, lesioning the nigrostriatal projection results

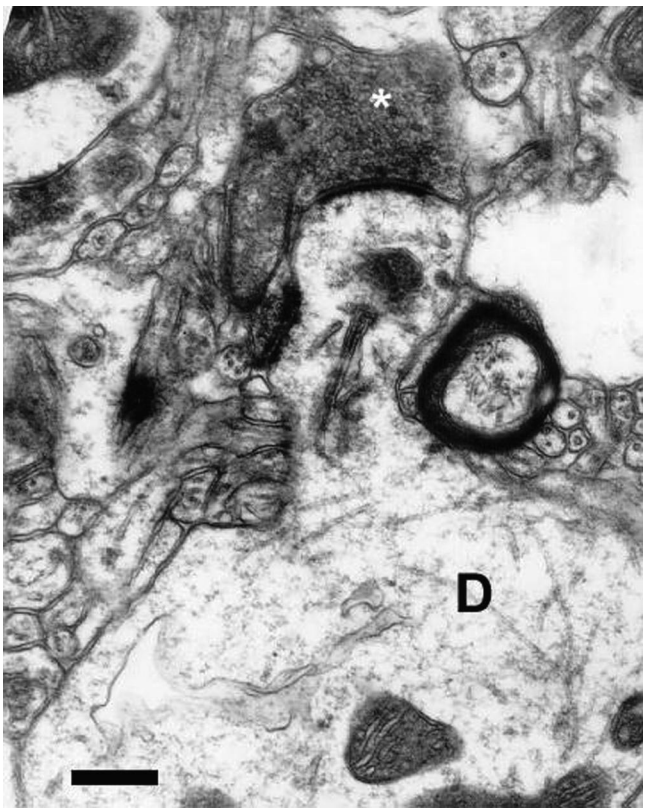



Fig. 9. A dendritic spine extends from a dendrite (D) in peritumorous cortex from human brain. The spine receives a synapse from a dark, presumably degenerating axon terminal (asterisk). Scale=500 nm.

in loss of synapses and spines on striatal neurons with an increase in the number of perforated synapses [128,129].

In addition to an overall reduction in spine density, other spine changes are seen following deafferentation. Spines with abnormal synaptic partners or axonless spines (Section 3.10) forming synapse-like junctions with glia are frequently seen [43,214]. Axonless spines are frequent initially but disappear after several days. Unusually long spines are also seen. These spines can exhibit multiple swellings along their length with multiple synaptic contacts. After loss of 75% of the parallel fiber axons in cerebellar cortex, Purkinje cell dendrites extend elongated, branched spines that synapse with the remaining axons [43].

Although deafferentation of spines leads to spine loss, under some circumstances destruction of other inputs can lead to spine increases. Loss of climbing fiber input to cerebellar Purkinje cells increases dendritic spine density [251]. Apparently, normal climbing fiber input limits the number of parallel fiber-related spines [250]. This heterosynaptic regulation may explain why an infarct in the cerebellar white matter would lead to increased spine density on Purkinje cells [79]. Similar spine alterations can also occur transneuronally. For example, transection of corpus callosum leads to decreased spine density on pyramidal neurons in layers receiving the callosal afferents (III and V) of auditory cortex, but increased spine density in layer IV [285].

### *4.2. Developmental deafferentation and agenesis*

Loss of the principal afferents to spiny neurons during early development produces many of the same alterations in dendritic spines as seen with deafferentation in the mature CNS. Corpus callosum sectioning at birth leads to 30% spine loss after 30 days [104]. An equally significant amount of spine loss is seen in visual cortex following eye removal or lesioning lateral geniculate nucleus at birth [102], and in auditory cortex following inner ear destruction at birth [179]. Adult spine reductions resulting from developmental injury can be less severe than those produced by adult injury, due to the increased plasticity of the developing brain [230].

While these experimental manipulations would appear to be relevant only to cases of injury, the developing brain is vulnerable to many insults affecting neuronal proliferation, migration, and survival [141]. Even a brief exposure to a disease or toxin can have serious developmental consequences if it occurs when a particular class of neurons is proliferating, thereby reducing the number of these neurons and deafferenting their target neurons. Insults during the fifth gestational week may contribute in this way to autism [53]. Disruption of the proliferation of cerebellar granule cells during the third trimester may lead to hyperactivity and attention deficit disorders in humans [3,204].

Cerebellar granule cells are also reduced by exposure to radiation [4], hypothyroidism [151], viral infection [18,139,158], and ethanol [162]. Genetic disorders resulting in granule cell agenesis in humans are known, but rare [81]. A number of mutations produce this condition in mice where it is easily studied [215,250]. Purkinje cells developing in the absence of granule cell axons still have dendritic spines. These spines exhibit many of the same alterations seen following deafferentation of adult Purkinje cells (Section 4.1). There are numerous giant spines [81,168], unusually long spines [158], and axonless spines making synapse-like junctions on glia [5,122,168]. These axonless spines persist in agranular cerebellum into old age [215]. It is not clear why axonless spines persist after agenesis more so than after deafferentation in the mature cerebellum. One possibility is developmental arrest of a postsynaptic maturation process. As mentioned in Sections 3.4 and 3.10, it is also not known whether these abnormal spines are transient structures similar to filopodia or relatively stable like mature spines. Increased motility of these protrusions would be expected in the case of developmental arrest.

### *4.3. Malnutrition*

Malnutrition can have severe consequences for both the

mature and developing brain. Malnutrition during development can lead to neuronal loss through effects on neuronal proliferation and survival. In severe cases, the ultimate outcome can be reduced brain growth, hydrocephalus, and mental retardation [217]. In the adult, prolonged malnutrition can produce neuron loss and eventually dementia.

Iodine deficiency, and the resulting thyroid hormone deficiency, is one of the most common preventable causes of mental retardation and cerebral palsy [57]. Hypothyroidism during brain development results in neuronal cell loss [165], with a subsequent loss of spines on the target spiny neurons. In the cerebellum, hypothyroidism during granule cell proliferation and migration results in widespread loss of these neurons [151]. As a consequence, Purkinje cell dendrites and dendritic spines are underdeveloped. Spine loss on cortical pyramidal neurons has been frequently observed in young hypothyroid animals [226], as well as after adult-onset iodine deficiency [194].

Like hypothyroidism, protein–calorie malnutrition during development can severely affect neuronal proliferation and brain growth resulting in mental retardation. Spine loss has been observed in pyramidal neurons in motor, somatosensory, and visual cortex [25,155]. This spine loss is accompanied by a persistence of very long spines [25,241]. Protein malnutrition results in a significant reduction in the number of spines and thorny excrescences on the dendrites of CA3 pyramidal cells that receive input from dentate granule cells [97]. Dentate granule cells also exhibit fewer spines [48]. Protein malnutrition during development can also produce a reduction of cerebellar granule cells [49,119], with subsequent loss of Purkinje cell spines and compensatory giant spines [41].

Some forms of prolonged vitamin deficiency induce neuropathology in the mature CNS. Although the spine pathologies of specific vitamin deficiencies have not been fully described, they may be similar to those seen in chronic ethanol exposure [286] (Section 4.6). Thiamin deficiency leads to neuronal death [278] and the associated neurological deficits often seen in chronic alcoholics [109]. Although increased spine density has been reported in some regions [6,8], prolonged protein malnutrition in adult life can also lead to neuronal death and a loss of synapses on target neurons [7,161].

### *4.4. Genetic disorders associated with mental retardation*

Mutations and chromosomal aberrations that lead to mental retardation (Table 3) have consistently been associated with abnormalities in dendrite structure and in the shape and density of dendritic spines [125,126,137]. The lack of appropriate animal models for many of these conditions means that most these studies have been restricted to observations on postmortem material. Due to the long time-interval between exitus and an ultrastructural examination, very little data on ultrastructural changes in dendritic spines of mentally retarded individuals are available. The most consistent finding of the light microscopic studies is dendritic spine loss from neocortical, hippocampal and/or Purkinje neurons.

Examination of cerebral cortex in Down's syndrome reveals a reduction in the length and branching of the dendritic arbor, and a reduction in spine density [271]. This morphology is particularly pronounced in older patients when compared with age-matched controls [78,265,271,273]. Marin-Padilla [171], in a study of a 19-month-old Down's child, found three different patterns

Table 3
Some genetic disorders associated with mental retardation and spine pathology

| Disorder | Genetic defect | Spine pathology[a] | References |
|---|---|---|---|
| Down's syndrome | chromosome 21 trisomy | 3.1, 3.3, 3.4, 3.9 | [78,169,171,265,271,273] |
| Fragile-X syndrome | deficiency of FMR1 protein | 3.2, 3.4 | [120,130,297] |
| Lafora disease | mutation of EPM2 gene | 3.1 | [33] |
| Maple syrup urine disease | deficiency of branched-chain keto-acid decarboxylase | 3.1, 3.4 | [136] |
| Niemann–Pick disease | deficiency of sphingomyelinase | 3.1 | [118,289] |
| Patau syndrome | chromosome 13 trisomy | 3.4 | [169,170] |
| Phenylketonuria | deficiency of hepatic enzyme phenylalanine hydroxylase | 3.2 | [146] |
| Maternal phenylketonuria | fetal exposure to hyperphenylalaninemia | 3.1, 3.4 | [145,147] |
| Atypical phenylketonuria | deficiency of dihydropteridine reductase | 3.1, 3.4 | [272] |
| Puppet-like syndrome of Angelman | absence of maternal contribution to chromosome 15q11-q13 region | 3.1 | [132] |
| Rett syndrome | mutations of MECP2 gene | 3.1 | [24] |
| Tuberous sclerosis | mutations of TSC1 or TCS2 genes | 3.1, 3.9 | [164] |

[a] Listed by section number as in Tables 1 and 2.

of spine pathology in pyramidal neurons of motor cortex, in addition to a few essentially normal neurons. Some neurons were densely covered with long, tortuous spines. Other neurons were uniformly covered with short, thin spines that were abnormally small in volume. A third type of neuron exhibited significant spine loss, with the few remaining spines having very large heads and thin necks. A pattern of small spines in neonates and abnormally long spines in older infants has been observed in more extensive studies of Down's syndrome [273].

Spine loss with an increase in very long (4–8 μm) protrusions has been reported in cases of mental retardation of unknown etiology [211,212]. The long, tortuous appearance of these protrusions contrasts sharply with normal spines observed in age-matched controls (Fig. 3). Many of the protrusions have prominent swellings at their tips or fusiform dilations along their lengths. These swellings may indicate the presence of synaptic contacts (Section 2). Purpura [211], in one of the few studies to include electron microscopy, has reported that these swellings receive synapses from apparently normal presynaptic axonal terminals. Unusually long, tortuous spines occur in many other forms of mental retardation, including Patau syndrome [169], fragile-X syndrome [297], maple syrup urine disease [136], and fetal alcohol syndrome [75].

The similarity of spine pathology in different conditions associated with mental retardation is striking. This correspondence has lead to the recent suggestion that the different genetic deficits associated with mental retardation disrupt a common signaling pathway related to the development of the dendritic cytoskeleton [137,216]. This hypothesis is difficult to reconcile with the wide variety of mutations implicated (Table 3). Even amino acid metabolism mutations, which produce mental retardation only when amino acids build up to toxic levels, exhibit the characteristic spine pathology. Furthermore, the same pathologies are seen in mental retardation caused by hypothyroidism or malnutrition (Section 4.3). Perhaps few, if any, of these conditions involve a direct deficit in spine-related functions. However, certain X chromosome-linked mutations implicated in mental retardation disrupt proteins involved in dendritic signaling. Of particular interest has been FMRP, the protein deficient in fragile-X syndrome, and Rho-related proteins involved in regulating the actin cytoskeleton and cytokinesis [216].

In fragile-X syndrome the abnormal abundance of long, thin protrusions occurs in conjunction with an increased spine density that apparently persists throughout life [120,130,297]. This is suggestive of a prolonged active filopodia stage, reminiscent of the persistent axonless spines in agranular cerebellum, described above. Evidence from fragile-X knockout mice suggests that this might not be the case, however, since filopodia do not persist abnormally during development [192], and yet a higher density of longer and thinner filopodia-like protrusions are found in the adult mutant [51].

### *4.5. Hypoxia or ischemia*

Brain tissue is highly-dependent on blood oxygen and glucose. Just 2 min of ischemia leads to a severe depletion of neuronal ATP [89], consequential loss of ion homeostasis, and continual depolarization [157]. Twenty minutes of hypoxia leads to the formation of dendritic varicosities [198], with corresponding loss of spines (Section 3.5). This pattern of dendritic injury is blocked by glutamate antagonists, and reproduced by 5 min exposure to glutamate agonists [117,198], suggesting that the dendritic injury is due to excitotoxicity.

As mentioned in Section 3.5, dendrites beaded by excitotoxicity can often recover, however the long-term consequences of an ischemic episode as short as 5 min can be the eventual death of some neurons in the brain [157]. Since deafferentation studies have established that the loss of the source of axons to spiny neurons leads to spine loss, it is perhaps not surprising that ischemia-induced neuronal death leads to decreased spine density. Spine loss has been described in Purkinje cells of fetal sheep [220], rat hippocampal pyramidal neurons [208], rat caudate neurons [193], and in pyramidal neurons of sensory-motor cortex [1], several days after hypoxic or ischemic insults. These insults were applied during early development, and in some cases spine loss recovered within a few weeks. However, ischemic lesions due to stroke in mature CNS can produce more permanent spine loss [58].

### *4.6. Alcohol and drug abuse*

Chronic ethanol consumption in a nutritionally adequate diet can lead to dendritic spine pathology. Loss of spines in neocortical or hippocampal pyramidal cells and in cerebellar Purkinje cells is the most usual finding [74,154,274,288]. Elongated and enlarged spines [274,292,293], dilation of smooth endoplasmic reticulum in spines [62], and shorter spines [154] have also been observed. In some studies no change [34,35,153], or increased spine density [76], has been found on some neurons. Spine density sometimes recovers during withdrawal [154].

As already discussed, a contributing factor to spine loss can be neuronal death and the consequent loss of afferents to spines. Chronic ethanol consumption in adult animals results in neuronal loss in hippocampus [35,153] and cerebellum [288]. Interestingly, megadoses of thiamin during chronic ethanol exposure that prevent this neuronal death also prevent spine loss and enlargement, suggesting that spine pathology in chronic ethanol exposure is due to afferent loss [294].

Exposure of the fetus to ethanol can produce a characteristic form of mental retardation known as fetal alcohol syndrome. A child with fetal alcohol syndrome had cortical pyramidal neurons with reduced spine density and

a predominance of long spines [75]. Animal models of fetal alcohol syndrome, created by feeding ethanol to pregnant rats or guinea pigs, demonstrate spine and synapse loss in cerebral cortex [69,96,144,159,233,246,264], although one study found increased spine density with many abnormally-shaped spines [183]. Abnormally long and tortuous dendritic spines [96,264], as well as persistent somatic spines on Purkinje cells [184], have also been observed in animal models of fetal alcohol syndrome.

As mentioned above, ethanol affects neural proliferation, but it does so in a bimodal manner [162]. Depending on the time and dosage, ethanol exposure can accelerate or depress proliferation. The most frequently reported result of fetal alcohol exposure is decreased numbers of neurons [17,28,167,183,275]. This neuronal loss may partially deafferent spiny neurons in fetal alcohol syndrome leading to the observed spine pathology, but the degree of deafferentation has never been directly studied.

Repeated experience with other addictive drugs also leads to spine pathology. Exposure to the stimulatory drugs amphetamine or cocaine leads to dendritic hypertrophy and increased spine density on the principal neurons of the nucleus accumbens and pyramidal neurons in prefrontal cortex [224]. The analgesic morphine, on the other hand, leads to dendritic atrophy and decreased spine density on these same neurons [225].

### *4.7. Poisoning*

As with ethanol, chronic exposure to a variety of other toxins during development can affect neuronal proliferation, survival, and ultimately spine density. For example, antimitotic drugs, glucocorticoid steroids, or lead poisoning can reduce the number of cerebellar granule cells [160,204]. Lead exposure, like ethanol exposure, can have bimodal effects on cell proliferation [87]. This may explain why some studies find increases in spine density with lead poisoning [200,201] while others find spine loss [142]. Developmental exposure to chlorine dioxide causes spine loss in neocortical pyramidal neurons [279]. Mercury poisoning during development produces spine loss with long and tortuous residual spines [196,263].

Acute exposure to some toxins can produce rapid spine changes. Soman poisoning results in convulsions and an 80% reduction in dendritic spines on the basal dendrites of CA1 pyramidal cells within 1 h [36]. Other convulsants produce similar acute effects [131,195]. Convulsant-induced spine loss may be due to excitotoxicity, since application of a glutamate receptor agonist to these neurons in culture leads to spine loss and dendritic varicosities within 5–30 min [110,117], just as seen in prolonged anoxia [198].

### *4.8. Epilepsy*

Examination of patients suffering from temporal lobe epilepsy reveals substantial spine pathologies in the brain foci of seizures. The most frequent and obvious change in the hippocampus is a loss of dendritic spines [239]. Large portions of dendrites are devoid of spines, with a few remaining spiny patches. Dendrites also frequently exhibit periodic varicosities, or patterns of beading. Occasionally elongated spines are seen with large and complex heads. In one case of Lennox–Gastaut syndrome, a childhood epileptic disorder associated with mental retardation, neocortical pyramidal neurons were found to have fewer spines [221]. Temporal lobe epilepsy patients generally also show loss of pyramidal neurons in hippocampus and entorhinal cortex [63,239].

Convulsant-treated animals, as models for epilepsy, show decreased spine density as a major effect [131,134]. Immediately after an induced epileptic seizure in naive animals there is spine loss, dendritic swelling, and evidence of excitotoxic neuron death [68,131]. The initial pathology is followed by complex structural changes that may contribute to the reoccurrence of seizures. In dentate gyrus, where deafferentation is usually followed by sprouting and recovery (Section 4.1), convulsion-induced spine reductions recover in conjunction with mossy fiber collateral sprouting [131,195]. However, signs of pathology also continue to be present with decreased spine density on pyramidal neurons [134], and electron-dense spines on degenerating dendrites [65].

Convulsant application to hippocampal slice cultures has also been used to study mechanisms of epilepsy [61,188,276]. Epileptiform activity in these slices produces up to 40% reduction in dendritic spines. This spine loss, as well as the observed pyramidal neuron degeneration, can be partially prevented by glutamate receptor antagonists [276].

### *4.9. Traumatic injury, tumors, and edema*

Traumatic injury to the brain or spinal cord that lesions axons can lead to spine pathology by two routes: anterograde axonal degeneration as discussed in Section 4.1, and retrograde degeneration of the neurons whose axons were severed [219]. Axotomized neurons often develop a shrunken, dark appearance with dendritic atrophy and loss of dendritic protrusions [2,30,280]. Many of these neurons die, but this depends on the extent of target deprivation and other factors [172,219]. Concussive brain injury can produce diffuse axonal damage that leads to severance of axons, and anterograde and retrograde degeneration [209]. This axonal damage is apparently due to the disassembly of microtubules and disruption of axonal transport. Relatively little evidence is available for transport-related dendritic damage but dendrites do show the same immediate argyrophilia as mechanically-damaged axons [95]. Varicose dendrites, possibly due to the accompanying ischemia and edema, have been noted after trauma [37,95,90,219].

Brain edema often produces focal hydropic swelling of dendritic trunks (Section 3.5). Dendritic varicosities with swollen or retracted spines are found in the edematous neuropil surrounding traumatic lesions or tumors [38,46,257]. Dendritic varicosities and associated spine loss are also seen in neocortical neurons of rats with experimentally induced hydrocephalus [178].

A variety of other spine changes can be seen in injured brain tissue [38,257]. Electron-dense spines (Section 4.7) can be found on dying neurons in edematous brain tissue [38] and near brain tumors [257]. The spine apparatus can be fragmented, dilated or hypertrophic (Fig. 6). Spines can also be enlarged with hypertrophic endosomal compartments or a hypertrophic cytoskeleton (Fig. 10).

### *4.10. Transmissible diseases*

Any disease that severely taxes the health of the body has potential consequences for neuronal health and survival, and therefore might be expected to induce some forms of spine pathology. As mentioned above, bacterial and viral infections during brain development can lead to loss of neurons and subsequent mental defects. For example, viral infections in the fifth week of gestation have been implicated in neuronal loss leading to autism [47,53]. The mature CNS is also vulnerable to infections. Bacterial infections of the brain and cerebral spinal fluid can lead to neuronal death, especially in hippocampus and neocortex [191]. Viruses may infect the central nervous system producing neuronal loss and even dementia and death [190,210]. Particularly notorious are lentiviruses such as human immunodeficiency virus and lyssaviruses causing rabies. Lentiviral infections produce decreased spine density in neocortical pyramidal cells [175,187], and a global reduction in spine length [185]. Focal swelling of dendrites, progressing to spongiform encephalopathy, has been reported in rabies [40].

Dendritic spine loss has also been observed in neocortical and hippocampal pyramidal neurons, and cerebellar Purkinje cells in prion diseases such as Creutzfeldt–Jakob disease and scrapie [15,29,39,72,79,123,135,140]. Prionoses show characteristic neuron loss [15,19,133]. In the cerebellum large numbers of granule cells can be lost with consequent deafferentation of Purkinje cells [26,148]. In these cases, Purkinje neurons have polymorphic spines and axonless spines completely ensheathed by astrocytic processes. The progression of transmissible human spongiform encephalopathy (kuru), as evaluated in monkeys inoculated from diseased human brain [19,20], is particularly enlightening. Eight weeks after inoculation Purkinje neurons exhibited normal numbers of spiny branchlets, with normal spine density and no elongated spines. Neuron loss began to be evident at 8 weeks and increased progressively. At 13 weeks, spine density was dramatically increased with large numbers of elongated spines. Elongated spines with tortuous necks persisted at 22, 40 and 94 weeks post-inoculation, while the number of spiny branchlets decreased progressively during this time. Spine density on the remaining branchlets remained above normal at 22 and 40 weeks. At 94 weeks post-inoculation, spine density was far below normal on the remaining dendrites. The progression of neuron loss accompanied first by spine proliferation and elongation, and subsequently by dendritic atrophy and spine loss, is suggestive of spine pathology as a compensatory response to axon loss in prionosis.

### *4.11. Progressive neurodegenerative diseases*

Neurodegeneration is common in aging. According to

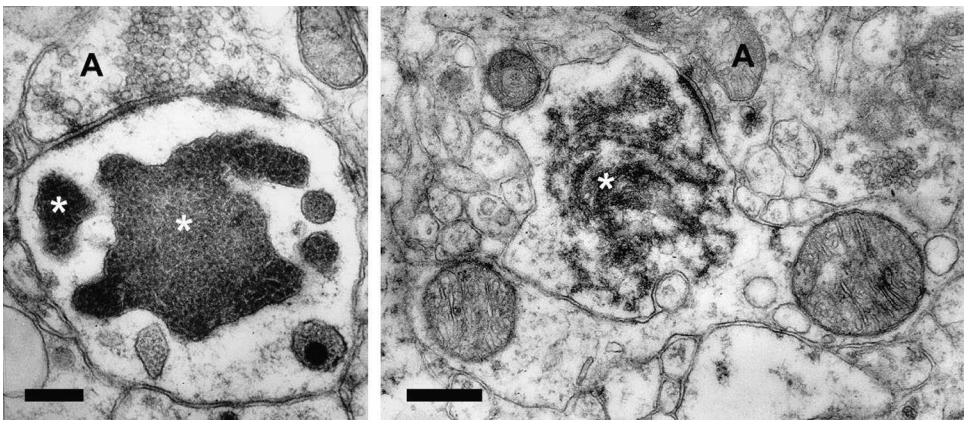



Fig. 10. Hypertrophy of spine organelles in human epitumorous cortex. Left: An enlarged dendritic spine from human peritumorous neocortex synapses with a normal looking axon terminal (A). The spine is filled with multiple, large multivesicular bodies (asterisks). Scale=200 nm. Right: A dendritic spine from human peritumorous neocortex synapses with an axon terminal (A). The spine contains aglomerrations of finely filamentous cytoskeletal material (asterisk), perhaps belonging to dense plates of a spine apparatus. Scale=300 nm. (Reprinted with permission from Ref. [257]. Copyright 1987 Springer-Verlag).

Peters et al. [207], layer I of prefrontal cortex becomes significantly thinner due to 30–60% reduction in density of synapses per unit volume in old monkeys. This loss is accompanied by a reduction in the number of apical dendrites and their spines indicating age-related degenerative changes of pyramidal cells. These changes are significantly correlated with the Cognitive Impairment Index and behavioral data. Patterns of 'normal' aging overlap considerably with the more severe conditions leading to dementia [205]. Dementia in Alzheimer's, Pick's, Huntington's, and Parkinson's diseases, and in multiple infarct patients, are all associated with neuronal death in cortical and/or subcortical structures, and with a loss of dendritic spines.

There is a progressive loss of dendritic spines from hippocampal pyramidal neurons in Alzheimer's disease [67,78,236]. Spines are also lost from dentate granule cells [58,66,99], and neocortical pyramidal neurons [14,39,237]. The synapse loss in Alzheimer's disease is accompanied by a compensatory increase in synapse size [234,235]. Frontal dementia also exhibits neuron loss and extensive spine loss in cortex [16]. Spine loss in neocortical neurons also accompanies other progressive neurodegenerative diseases such as Pick's disease [71] and motor neuron disease [80].

Loss of dopaminergic neurons from the substantia nigra is a hallmark of Parkinson's disease. The striatal neurons that normally receive this dopaminergic projection exhibit fewer dendritic spines in Parkinson's disease [181], similar to the effects of deafferentation by lesion of the nigrostriatal projection discussed in Section 4.1. Spine loss is also seen in neurons of locus ceruleus and substantia nigra in Parkinson's disease [202,203]. Striatal neurons in Huntington's disease show increased spine density in moderate cases, but decreased spine density in severe cases [70]. Transgenic mice expressing mutant huntingtin also exhibit spine loss from striatal and cortical neurons [108].

Given that oxidative stress may contribute to a number of progressive neurodegenerative diseases [11,100], it seems relevant to mention here that reactive oxygen species can produce spine pathology. Rat hippocampal CA1 pyramidal neurons show spine loss 1 day after oxidative stress induced by a 4 h exposure to ozone [10]. Similar spine loss is seen in prefrontal cortex, striatum, and olfactory bulb, with vacuolation of dendrites and spines [9,50].

### *4.12. Schizophrenia*

Decreased spine density has been found in schizophrenic subjects in pyramidal cells of temporal and frontal cortex [98]. Smaller spines have been reported in the striatum of schizophrenics [223]. These findings may be confounded by use of antipsychotic drugs. Chronic exposure to the antipsychotic drug haloperidol in rats can lead to reduced spine density [138]. In a study with controls for the effects of antipsychotic medications, spine loss was seen in dorsolateral prefrontal cortex [101]. This decreased spine density appears to reflect a reduction of excitatory inputs due to neuronal loss in mediodorsal thalamic nucleus.

### *4.13. Abnormal hormone levels*

Abnormal levels of thyroid, gonadal and adrenal hormones are known to induce spine pathology. Some aspects of thyroid hormone deficiency have been already mentioned in the context of malnutrition. Hypothyroidism during brain development results in reduced spine density on spiny neurons in adulthood [227], through effects on cell proliferation [151] and axonal growth [287]. These deficits can be prevented by thyroxine treatment provided it begins early enough in development [229]. Adult thyroidectomy leads to spine loss from cortical pyramidal cells [228]. Hyperthyroidism leads to spine loss in hippocampal pyramidal cells in adult animals as well [106], and to developmental deficits similar to hypothyroidism [151].

Spine density in some brain regions fluctuates by 30% during the female reproductive cycle in response to changing levels of ovarian hormones [242,301]. Ovariectomy results in a sustained lower spine density on CA1 pyramidal cells [300], and in hypothalamic neurons [91]. However, gonadectomy in male rats results in increased spine density in hypothalamus [55,92].

While acute stress can increase hippocampal spines in male rats [242], prolonged stress appears to produce hippocampal atrophy through the action of adrenal hormones [232]. Chronic exposure to stress or stress hormones, results in atrophy of the dendritic arbor of CA3 pyramidal cells [166,291,302]. This dendritic atrophy is accompanied by atrophy of axonal afferents from dentate granule cells, resulting in a decrease in the total number of dendritic synapses but no decrease in spine density on CA3 neurons [253,266]. Loss of spines in neocortical and hippocampal pyramidal neurons has been reported in mice with autoimmunity-associated behavioral syndrome resembling animals exposed to chronic stress [231]. Adrenalectomy results in dentate granule cell loss and similar synaptic loss on CA3 neurons as described for stress [156,254].

## 5. Discussion

### *5.1. Data reliability*

In reviewing such a broad literature we have included data obtained by a large variety of methods with varying degrees of reliability. Most human tissue, being post-

mortem material, was analyzed with rapid Golgi impregnation. Golgi techniques were also widely used in animal experiments for quantitative estimations of spine density. The non-uniformity of Golgi impregnation [126,296] and the difficulty of counting spines in light microscopy no doubt introduces some inaccuracies in the results. For example, some studies report spine densities of only 0.3 spines per μm of dendrite in control dentate granule cells [6,8], whereas other Golgi studies report much higher spine densities of 1 spine per μm [59]. Thus, spines may not be fully impregnated and/or counted in all cases. For reliable conclusions, control tissue should always be prepared for comparison. Even then, small increases or decreases in numbers of dendritic spines will be very difficult to detect by light microscopy.

Similarly problematic are single-section electron microscopic studies used to quantify changes in spine shape, in spine head size, in the lengths and diameters of spine necks, and in the size, shape and distribution of synapses [98,111]. Rarely have the appropriate three-dimensional techniques been applied to these problems. Many findings will remain controversial until serial section analyses and unbiased stereological techniques are employed.

Another issue is the time interval between withdrawal and fixation of postmortem brain tissue [126]. Typical delays place substantial burdens on the health of the neurons. Ramon y Cajal noted that it is possible to watch 'before ones eyes' the swelling of dendrites and resorption of spines during the first half-hour after exitus [218]. Biopsy material, fixed quickly, is surely much better preserved. In any case, an anoxia of several minutes as well as possible mechanical injury must be taken into consideration as it could negatively influence spine structure.

Also critical is the timing of measurements in relationship to the stage of a disease, age of patient, sex and even time of reproductive cycle. Spine loss and gain is a continually ongoing, normal brain process, such as in the hippocampal variation during the estrus cycle [299]. These ongoing variations place added importance to experimental timing and careful controls.

Obviously, no one biopsy or postmortem sample can be taken as proof of spine pathology associated with a condition. However, most studies compared a number of samples to similarly prepared samples from normal patients. Based on such findings replicated in multiple studies and animal experiments, the types of spine pathology we have reviewed and classified are supported by substantial evidence. Taken together the data show that consistent spine pathology occurs in many disorders independent of the methods used and is not just an artifact of suboptimal postmortem fixation as recently suggested [94].

### *5.2. Common causes*

Some aspects of spine pathology are commonly found in a large number of conditions. This is especially true of spine loss and elongation, which have both been found in deafferentation, neuronal agenesis, malnutrition, alcohol abuse, poisoning and spongiform encephalopathy (Table 1), as well as in many forms of mental retardation (Table 3). These similar spine pathologies in very different conditions raise the question of whether common causes exist. Does the spine pathology in mental retardation arise from similar causes as the spine pathology in deafferentation, for example?

One possibility suggested for the common spine pathologies seen in various forms of mental retardation is a developmental defect intrinsic to dendrites and spines [125,137]. This hypothesis interprets the spine pathologies seen in most types of mental retardation as abnormal functioning of the spiny neuron. But the characteristic pattern of alterations is found in too large a variety of conditions to think that these changes represent failures of the postsynaptic cell alone. Given that selective deafferentation can produce analogous abnormalities in the target neurons (Sections 4.1 and 4.2), the data appears to support an alternative view in which the spiny neuron is functioning normally in abnormal conditions.

In this alternative hypothesis the characteristic spine pathology seen in conditions such as mental retardation would be due primarily to a loss of afferent axons. As in acute deafferentation, spines that have lost axonal synapses would retract and spine density would consequently decrease. The loss of afferents might also provoke normal (though exaggerated) compensatory mechanisms. In some cases, spines might be stabilized by lower affinity synapse-like junctions with glial or non-axonal neuronal components. The lower density of axons in the vicinity of afflicted neurons might also provoke elongation of spines in an effort to reach the axons that are now farther away. Spines that succeed in making high affinity synaptic contacts might also become enlarged to increase the now deficient excitatory input.

Taken as a whole the data indicate that spine loss occurs when there is widespread neuronal loss. Neuron loss would at least partially deafferent spiny neurons. Significant deafferentation would be expected to produce the characteristic spine pathology of decreased spine density, long and tortuous spines, and aberrant and enlarged synapses. Other studies have also recognized that the synapse loss in Alzheimer's and other neurodegenerative diseases is attributable to deafferentation by neuron loss [150,292]. In some cases the locus of spine loss can serve as a guide as to which afferents are missing and therefore which regions of the brain are deficient in neurons, as previously suggested by Scheibel and Scheibel [238]. Spine pathology might also be exacerbated by a loss of adequate mechanisms, like neurogenesis or axonal sprouting, that normally compensate for neuronal loss in the mature brain. Given evidence of elongated, tortuous, and giant spines, we would argue that postsynaptic compensatory mechanisms are functioning, but maintenance of afferents may be defective.

Golgi studies and fluorescent microscopy studies need to be extended with ultrastructural studies to verify the fate of synapses and to assess the role of the pathological spine in bridging the distance between dendrite and axon. Three-dimensional ultrastructural studies would be able to assess the distribution of axons in the vicinity of afflicted dendrites. A sparser distribution of axons, with elongated spines reaching out to these few remaining inputs, would provide strong evidence that the afferent distribution contributes to distortions of spine shape. In support of this hypothesis, fluorescent labeling for synaptophysin reveals a decrease in axon labeling in regions of spine pathology in both Rett syndrome [23,24] and in transmissible spongiform encephalopathy [21]. However, to determine if the longer spines make synapses, serial electron microscopy would appear to be required [84].

Detailed studies are needed to detect differences in the spine pathologies of different disorders. The effects of acute deafferentation may look superficially similar to spine pathology in a particular form of mental retardation, but ultrastructural investigation may reveal that the spine abnormalities are really quite different. Similarly, some forms of mental retardation may have very different spine pathologies, but too few detailed studies are available to determine whether differences exist.

## 6. Conclusions

The present classification of spine pathologies is no doubt incomplete. Many forms remain to be described in detail. Two main types of spine pathology appear to commonly arise. One type of pathology appears to be due to disruption of neuronal connectivity, such as following deafferentation. This pathology is most frequently characterized by the spine loss and disordered spine morphology commonly seen with light microscopy. The other type of pathology follows injury to or alterations in the neuron on which the spine resides. This pathology is characterized most often by a change in the ultrastructural composition of the spine, though dramatic changes in dendritic structure, such as focal swelling, are sometimes visible even with light microscopy.

Pathology of dendritic spines may seem like an overly specialized area, but given the centrality of spines to excitatory input in principal neurons, it is emerging as an unusually important branch of neuropathology. Studying the pathology of dendritic spines will undoubtedly contribute to understanding both the pathogenic aspects of central nervous system disease and normal dendritic spine function.

## References

[1] V.A. Akulinin, S.S. Stepanov, V.V. Semchenko, P.V. Belichenko, Dendritic changes of the pyramidal neurons in layer V of sensory-motor cortex of the rat brain during the postresuscitation period, Resuscitation 35 (1997) 157–164.
[2] N.A. Al-Abdulla, C. Portera-Cailliau, L.J. Martin, Occipital cortex ablation in adult rat causes retrograde neuronal death in the lateral geniculate nucleus that resembles apoptosis, Neuroscience 86 (1998) 191–209.
[3] J. Altman, Morphological and behavioral markers of environmentally induced retardation of brain development: an animal model, Environ. Health Perspect. 74 (1987) 153–168.
[4] J. Altman, W.J. Anderson, Experimental reorganization of the cerebellar cortex. I. Morphological effects of elimination of all microneurons with prolonged X-irradiation started at birth, J. Comp. Neurol. 146 (1972) 355–406.
[5] J. Altman, S. Bayer, Development of the Cerebellar System: In Relation to Its Evolution, Structure, and Functions, CRC Press, Boca Raton, FL, 1997.
[6] J.P. Andrade, A.J. Castanheira-Vale, P.G. Paz-Dias, M.D. Madeira, M.M. Paula-Barbosa, The dendritic trees of neurons from the hippocampal formation of protein-deprived adult rats. A quantitative Golgi study, Exp. Brain Res. 109 (1996) 419–433.
[7] J.P. Andrade, M.D. Madeira, M.M. Paula-Barbosa, Effects of long-term malnutrition and rehabilitation on the hippocampal formation of the adult rat, J. Anat. 187 (1995) 379–393.
[8] J.P. Andrade, M.D. Madeira, M.M. Paula-Barbosa, Differential vulnerability of the subiculum and entorhinal cortex of the adult rat to prolonged protein deprivation, Hippocampus 8 (1998) 33–47.
[9] M.R. Avila-Costa, L. Colin-Barenque, T.I. Fortoul, P. Machado-Salas, J. Espinosa-Villanueva, C. Rugerio-Vargas, G. Borgonio, C. Dorado, S. Rivas-Arancibia, Motor impairments in an oxidative stress model and its correlation with cytological changes on rat striatum and prefrontal cortex, Int. J. Neurosci. 108 (2001) 193–200.
[10] M.R. Avila-Costa, L. Colin-Barenque, T.I. Fortoul, P. Machado-Salas, J. Espinosa-Villanueva, C. Rugerio-Vargas, S. Rivas-Arancibia, Memory deterioration in an oxidative stress model and its correlation with cytological changes on rat hippocampus CA1, Neurosci. Lett. 270 (1999) 107–109.
[11] J.S. Bains, C.A. Shaw, Neurodegenerative disorders in humans: the role of glutathione in oxidative stress-mediated neuronal death, Brain Res. Rev. 25 (1997) 335–358.
[12] B.W. Bakkum, L.A. Benevento, R.S. Cohen, Effects of light/dark- and dark-rearing on synaptic morphology in the superior colliculus and visual cortex of the postnatal and adult rat, J. Neurosci. Res. 28 (1991) 65–80.
[13] S.J. Baloyannis, S.U. Kim, Experimental modification of cerebellar development in tissue culture: x-irradiation induces granular degeneration and unattached Purkinje cell dendritic spines, Neurosci. Lett. 12 (1979) 283–288.
[14] S.J. Baloyannis, S.L. Manolidis, L.S. Manolidis, The acoustic cortex in Alzheimer's disease, Acta Otolaryngol. Suppl. 494 (1992) 1–13.
[15] S.J. Baloyannis, S.L. Manolidis, L.S. Manolidis, Synaptic alterations in acoustic cortex in Creutzfeldt–Jacob disease, Acta Otolaryngol. 115 (1995) 202–205.
[16] S.J. Baloyannis, S.L. Manolidis, L.S. Manolidis, The acoustic cortex in frontal dementia, Acta Otolaryngol. 121 (2001) 289–292.
[17] D.E. Barnes, D.W. Walker, Prenatal ethanol exposure permanently reduces the number of pyramidal neurons in rat hippocampus, Brain Res. 227 (1981) 333–340.
[18] J.R. Bautista, S.A. Rubin, T.H. Moran, G.J. Schwartz, K.M. Carbone, Developmental injury to the cerebellum following perinatal Borna disease virus infection, Brain Res. Dev. Brain Res. 90 (1995) 45–53.
[19] E. Beck, I.J. Bak, J.F. Christ, D.C. Gajdusek, C.J. Gibbs Jr., R. Hassler, Experimental kuru in the spider monkey. Histopathological and ultrastructural studies of the brain during early stages of incubation, Brain 98 (1975) 595–612.
[20] E. Beck, P.M. Daniel, A.J. Davey, D.C. Gajdusek, C.J. Gibbs Jr., The pathogenesis of transmissible spongiform encephalopathy: an ultrastructural study, Brain 105 (1982) 755–786.

[21] P.V. Belichenko, D. Brown, M. Jeffrey, J.R. Fraser, Dendritic and synaptic alterations of hippocampal pyramidal neurones in scrapie-infected mice, Neuropathol. Appl. Neurobiol. 26 (2000) 143–149.
[22] P.V. Belichenko, A. Dahlstrom, Studies on the 3-dimensional architecture of dendritic spines and varicosities in human cortex by confocal laser scanning microscopy and Lucifer yellow microinjections, J. Neurosci. Methods 57 (1995) 55–61.
[23] P.V. Belichenko, B. Hagberg, A. Dahlstrom, Morphological study of neocortical areas in Rett syndrome, Acta Neuropathol. (Berlin) 93 (1997) 50–61.
[24] P.V. Belichenko, A. Oldfors, B. Hagberg, A. Dahlstrom, Rett syndrome: 3-D confocal microscopy of cortical pyramidal dendrites and afferents, Neuroreport 5 (1994) 1509–1513.
[25] L. Benitez-Bribiesca, I. De la Rosa-Alvarez, A. Mansilla-Olivares, Dendritic spine pathology in infants with severe protein–calorie malnutrition, Pediatrics 104 (1999) e21.
[26] J. Berciano, M.T. Berciano, J.M. Polo, J. Figols, J. Ciudad, M. Lafarga, Creutzfeldt–Jakob disease with severe involvement of cerebral white matter and cerebellum, Virchows Arch. A Pathol. Anat. Histopathol. 417 (1990) 533–538.
[27] R.F. Berman, J.H. Hannigan, M.A. Sperry, C.S. Zajac, Prenatal alcohol exposure and the effects of environmental enrichment on hippocampal dendritic spine density, Alcohol 13 (1996) 209–216.
[28] R.F. Berman, J.H. Hannigan, Effects of prenatal alcohol exposure on the hippocampus: Spatial behavior, electrophysiology, and neuroanatomy, Hippocampus 10 (2000) 94–110.
[29] D. Brown, P. Belichenko, J. Sales, M. Jeffrey, J.R. Fraser, Early loss of dendritic spines in murine scrapie revealed by confocal analysis, Neuroreport 12 (2001) 179–183.
[30] A. Buffo, M. Fronte, A.B. Oestreicher, F. Rossi, Degenerative phenomena and reactive modifications of the adult rat inferior olivary neurons following axotomy and disconnection from their targets, Neuroscience 85 (1998) 587–604.
[31] M.C. Bundman, C.M. Gall, Ultrastructural plasticity of the dentate gyrus granule cells following recurrent limbic seizures: II. Alterations in somatic synapses, Hippocampus 4 (1994) 611–622.
[32] M.C. Bundman, R.M. Pico, C.M. Gall, Ultrastructural plasticity of the dentate gyrus granule cells following recurrent limbic seizures: I. Increase in somatic spines, Hippocampus 4 (1994) 601–610.
[33] H.L. Busard, W.O. Renier, F.J. Gabreels, H.H. Jaspar, J.L. Slooff, A.J. Janssen, U.J. Van Haelst, Lafora disease: a quantitative morphological and biochemical study of the cerebral cortex, Clin. Neuropathol. 6 (1987) 1–6.
[34] A. Cadete-Leite, M.C. Alves, M.M. Paula-Barbosa, H.B. Uylings, M.A. Tavares, Quantitative analysis of basal dendrites of prefrontal pyramidal cells after chronic alcohol consumption and withdrawal in the adult rat, Alcohol 25 (1990) 467–475.
[35] A. Cadete-Leite, M.A. Tavares, H.B. Uylings, M. Paula-Barbosa, Granule cell loss and dendritic regrowth in the hippocampal dentate gyrus of the rat after chronic alcohol consumption, Brain Res. 473 (1988) 1–14.
[36] P. Carpentier, M. Lambrinidis, G. Blanchet, Early dendritic changes in hippocampal pyramidal neurones (field CA1) of rats subjected to acute soman intoxication: a light microscopic study, Brain Res. 541 (1991) 293–299.
[37] O.J. Castejon, Electron microscopic analysis of cortical biopsies in patients with traumatic brain injuries and dysfunction of neurobehavioural system, J. Submicrosc. Cytol. Pathol. 30 (1998) 145–156.
[38] O.J. Castejon, C. Valero, M. Diaz, Synaptic degenerative changes in human traumatic brain edema. An electron microscopic study of cerebral cortical biopsies, J. Neurosurg. Sci. 39 (1995) 47–65.
[39] I. Catala, I. Ferrer, E. Galofre, I. Fabregues, Decreased numbers of dendritic spines on cortical pyramidal neurons in dementia. A quantitative Golgi study on biopsy samples, Hum. Neurobiol. 6 (1988) 255–259.
[40] K.M. Charlton, G.A. Casey, W.A. Webster, A. Bundza, Experimental rabies in skunks and foxes. Pathogenesis of the spongiform lesions, Lab. Invest. 57 (1987) 634–645.
[41] S. Chen, D.E. Hillman, Giant spines and enlarged synapses in Purkinje cells by malnutrition, Brain Res. 187 (1980) 487–493.
[42] S. Chen, D.E. Hillman, Marked reorganization of Purkinje cell dendrites and spines in adult rat following vacating of synapses due to deafferentation, Brain Res. 245 (1982) 131–135.
[43] S. Chen, D.E. Hillman, Plasticity of the parallel fiber–Purkinje cell synapse by spine takeover and new synapse formation in the adult rat, Brain Res. 240 (1982) 205–220.
[44] S. Chen, D.E. Hillman, Robust synaptic plasticity of striatal cells following partial deafferentation, Brain Res. 520 (1990) 103–114.
[45] H.W. Cheng, T. Jiang, S.A. Brown, G.M. Pasinetti, C.E. Funch, T.H. McNeill, Response of striatal astrocytes to neuronal deafferentation: an immunocytochemical and ultrastructural study, Neuroscience 62 (1994) 425–439.
[46] H.W. Cheng, J.A. Rafols, H.G. Goshgarian, Y. Anavi, J. Tong, T.H. McNeill, Differential spine loss and regrowth of striatal neurons following multiple forms of deafferentation: a Golgi study, Exp. Neurol. 147 (1997) 287–298.
[47] S. Chess, Follow-up report on autism in congenital rubella, J. Autism Child. Schizophr. 7 (1997) 69–81.
[48] L. Cintra, S. Diaz-Cintra, A. Galvan, T. Kemper, P.J. Morgane, Effects of protein undernutrition on the dentate gyrus in rats of three age groups, Brain Res. 532 (1990) 271–277.
[49] J. Clos, C. Favre, M. Selme-Matrat, J. Legrand, Effects of undernutrition on cell formation in the rat brain and specially on cellular composition of the cerebellum, Brain Res. 123 (1977) 13–26.
[50] L. Colin-Barenque, M.R. Avila-Costa, T. Fortoul, C. Rugerio-Vargas, J.P. Machado-Salas, J. Espinosa-Villanueva, S. Rivas-Arancibia, Morphologic alteration of the olfactory bulb after acute ozone exposure in rats, Neurosci. Lett. 274 (1999) 1–4.
[51] T.A. Comery, J.B. Harris, P.J. Willems, B.A. Oostra, S.A. Irwin, I.J. Weiler, W.T. Greenough, Abnormal dendritic spines in fragile X knockout mice: maturation and pruning deficits, Proc. Natl. Acad. Sci. USA 94 (1997) 5401–5404.
[52] A.I. Cowan, C. Stricker, L.J. Reece, S.J. Redman, Long-term plasticity at excitatory synapses on aspinous interneurons in area CA1 lacks synaptic specificity, J. Neurophysiol. 79 (1998) 13–20.
[53] E. Courchesne, Brainstem, cerebellar and limbic neuroanatomical abnormalities in autism, Curr. Opin. Neurobiol. 7 (1997) 269–278.
[54] M.E. Dailey, S.J. Smith, The dynamics of dendritic structure in developing hippocampal slices, J. Neurosci. 16 (1996) 2983–2994.
[55] S.C. Danzer, N.T. McMullen, N.E. Rance, Dendritic growth of arcuate neuroendocrine neurons following orchidectomy in adult rats, J. Comp. Neurol. 390 (1998) 234–246.
[56] K. Dekker-Ohno, S. Hayasaka, Y. Takagishi, S. Oda, N. Wakasugi, K. Mikoshiba, M. Inouye, H. Yamamura, Endoplasmic reticulum is missing in dendritic spines of Purkinje cells of the ataxic mutant rat, Brain Res. 714 (1996) 226–230.
[57] G.R. DeLong, Effects of nutrition on brain development in humans, Am. J. Clin. Nutr. Suppl. 57 (1993) 286S–290S.
[58] J.P. De Ruiter, H.B. Uylings, Morphometric and dendritic analysis of fascia dentata granule cells in human aging and senile dementia, Brain Res. 402 (1987) 217–229.
[59] N.L. Desmond, W.B. Levy, Granule cell dendritic spine density in the rat hippocampus varies with spine shape and location, Neurosci. Lett. 54 (1985) 219–224.
[60] R.M. Devon, D.G. Jones, Synaptic parameters in developing rat cerebral cortex: comparison of anaesthetized and unanaesthetized states, Dev. Neurosci. 4 (1981) 351–362.
[61] A. Drakew, M. Muller, B.H. Gahwiler, S.M. Thompson, M. Frotscher, Spine loss in experimental epilepsy: quantitative light and electron microscopic analysis of intracellularly stained CA3 pyramidal cells in hippocampal slice cultures, Neuroscience 70 (1996) 31–45.
[62] C.A. Dlugos, R.J. Pentney, Effects of chronic ethanol consumption

on SER of Purkinje neurons in old F344 rats, Alcohol 20 (2000) 125–132.
[63] F. Du, W.O. Whetsell, B. Abou-Khalil, B. Blumenkopf, E.W. Lothman, R. Schwarcz, Preferential neuronal loss in layer III of the entorhinal cortex in patients with temporal lobe epilepsy, Epilepsy Res. 16 (1993) 223–233.
[64] A. Dunaevsky, A. Tashiro, A. Majewska, C. Mason, R. Yuste, Developmental regulation of spine motility in the mammalian central nervous system, Proc. Natl. Acad. Sci. USA 96 (1999) 13438–13443.
[65] T. Eid, R. Schwarcz, O.P. Ottersen, Ultrastructure and immunocytochemical distribution of GABA in layer III of the rat medial entorhinal cortex following aminooxyacetic acid-induced seizures, Exp. Brain Res. 125 (1999) 463–475.
[66] G. Einstein, R. Buranosky, B.J. Crain, Dendritic pathology of granule cells in Alzheimer's disease is unrelated to neuritic plaques, J. Neurosci. 14 (1994) 5077–5088.
[67] K.H. El Hachimi, J.F. Foncin, Loss of dendritic spines in Alzheimer's disease, C. R. Acad. Sci. III 311 (1990) 397–402.
[68] M. Evans, T. Griffiths, B. Meldrum, Early changes in the rat hippocampus following seizures induced by bicuculline or L-allylglycine: a light and electron microscope study, Neuropathol. Appl. Neurobiol. 9 (1983) 39–52.
[69] I. Fabregues, I. Ferrer, J.M. Gairi, A. Cahuana, P. Giner, Effects of prenatal exposure to ethanol on the maturation of the pyramidal neurons in the cerebral cortex of the guinea-pig: a quantitative Golgi study, Neuropathol. Appl. Neurobiol. 11 (1985) 291–298.
[70] R.J. Ferrante, N.W. Kowall, E.P. Richardson Jr., Proliferative and degenerative changes in striatal spiny neurons in Huntington's disease: a combined study using the section-Golgi method and calbindin D28k immunocytochemistry, J. Neurosci. 11 (1991) 3877–3887.
[71] I. Ferrer, Neurons and their dendrites in frontotemporal dementia, Dement. Geriatr. Cogn. Disord. 10 (Suppl. 1) (1999) 55–60.
[72] I. Ferrer, F. Costa, J.M. Grau Veciana, Creutzfeldt–Jacob disease: a Golgi study, Neuropathol. Appl. Neurobiol. 7 (1981) 237–242.
[73] I. Ferrer, V. Cusi, M. Pineda, E. Galofre, J. Vila, Focal dendritic swellings in Purkinje cells in mucopolysaccharidoses types I, II and III. A Golgi and ultrastructural study, Neuropathol. Appl. Neurobiol. 14 (1988) 315–323.
[74] I. Ferrer, I. Fabregues, J. Rairiz, E. Galofre, Decreased numbers of dendritic spines on cortical pyramidal neurons in human chronic alcoholism, Neurosci. Lett. 69 (1986) 115–119.
[75] I. Ferrer, E. Galofre, Dendritic spine anomalies in fetal alcohol syndrome, Neuropediatrics 18 (1987) 161–163.
[76] I. Ferrer, E. Galofre, I. Fabregues, D. Lopez-Tejero, Effects of chronic ethanol consumption beginning at adolescence: increased numbers of dendritic spines on cortical pyramidal cells in the adulthood, Acta Neuropathol. (Berlin) 78 (1989) 528–532.
[77] I. Ferrer, N. Guionnet, F. Cruz-Sanchez, T. Tunon, Neuronal alterations in patients with dementia: a Golgi study on biopsy samples, Neurosci. Lett. 114 (1990) 11–16.
[78] I. Ferrer, F. Gullota, Down's syndrome and Alzheimer's disease: dendritic spine counts in the hippocampus, Acta Neuropathol. 79 (1990) 680–685.
[79] I. Ferrer, J. Kulisevski, J. Vazquez, G. Gonzalez, M. Pineda, Purkinje cells in degenerative diseases of the cerebellum and its connections: a Golgi study, Clin. Neuropathol. 7 (1988) 22–28.
[80] I. Ferrer, C. Roig, A. Espino, G. Peiro, X. Matias Guiu, Dementia of frontal lobe type and motor neuron disease. A Golgi study of the frontal cortex, J. Neurol. Neurosurg. Psychiatry 54 (1991) 932–934.
[81] I. Ferrer, J. Sirvent, J.M. Manresa, E. Galofre, E. Fernandez-Alvarez, M. Pineda, Primary degeneration of the granular layer of the cerebellum (Norman type). A Golgi study, Acta Neuropathol. (Berlin) 75 (1987) 203–208.
[82] J.C. Fiala, M. Feinberg, V. Popov, K.M. Harris, Synaptogenesis via dendritic filopodia in developing hippocampal area CA1, J. Neurosci. 18 (1998) 8900–8911.
[83] J.C. Fiala, K.M. Harris, Dendrite structure, in: G. Stuart, N. Spruston, M. Häusser (Eds.), Dendrites, Oxford University Press, Oxford, 1999, pp. 1–34.
[84] J.C. Fiala, K.M. Harris, Extending unbiased stereology of brain ultrastructure to three-dimensional volumes, J. Am. Med. Inform. Assoc. 8 (2001) 1–16.
[85] E. Fifkova, The effect of unilateral deprivation on visual centers in rats, J. Comp. Neurol. 140 (1970) 431–438.
[86] E. Fifkova, Actin in the nervous system, Brain Res. 9 (1985) 187–215.
[87] Y. Finkelstein, M.E. Markowitz, J.F. Rosen, Low-level lead-induced neurotoxicity in children; an update on central nervous system effects, Brain Res. Rev. 27 (1998) 168–176.
[88] M. Fischer, S. Kaech, D. Knutti, A. Matus, Rapid actin-based plasticity in dendritic spines, Neuron 20 (1998) 847–854.
[89] J. Folbergrova, P.-A. Li, H. Uchino, M.-L. Smith, B.K. Siesjo, Changes in the bioenergetic state of rat hippocampus during 2.5 min of ischemia, and prevention of cell damage by cyclosporin A in hyperglycemic subjects, Exp. Brain Res. 114 (1997) 44–50.
[90] M.M. Folkerts, R.F. Berman, J.P. Muizelaar, J.A. Rafols, Disruption of MAP-2 immunostaining in rat hippocampus after traumatic brain injury, J. Neurotrauma 15 (1998) 349–363.
[91] M. Frankfurt, E. Gould, C.S. Woolley, B.S. McEwen, Gonadal steroids modify dendritic spine density in ventromedial hypothalamic neurons: a Golgi study in the adult rat, Neuroendocrinology 51 (1990) 530–535.
[92] M. Frankfurt, B.S. McEwen, 5,7-Dihydroxytryptamine and gonadal steroid manipulation alter spine density in ventromedial hypothalamic neurons, Neuroendocrinology 54 (1991) 653–657.
[93] M. Freire, Effects of dark rearing on dendritic spines in layer IV of the mouse visual cortex. A quantitative electron microscopical study, J. Anat. 126 (1978) 193–201.
[94] Z. Galdzicki, R. Siarey, R. Pearce, J. Stoll, S.I. Rapoport, On the cause of mental retardation in Down syndrome: extrapolation from full and segmental trisomy 16 mouse models, Brain Res. Rev. 35 (2001) 115–145.
[95] F. Gallyas, G. Zoltay, An immediate light microscopic response of neuronal somata, dendrites and axons in non-contusing concussive head injury in the rat, Acta Neuropathol. 83 (1992) 386–393.
[96] E. Galofre, I. Ferrer, I. Fabregues, D. Lopez-Tejero, Effects of prenatal ethanol exposure on dendritic spines of layer V pyramidal neurons in the somatosensory cortex of the rat, J. Neurol. Sci. 81 (1987) 185–195.
[97] M. Garcia-Ruiz, S. Diaz-Cintra, L. Cintra, G. Corkidi, Effect of protein malnutrition on CA3 hippocampal pyramidal cells in rats of three ages, Brain Res. 625 (1993) 203–212.
[98] L.J. Garey, W.Y. Ong, T.S. Patel, M. Kanani, A. Davis, A.M. Mortimer, T.R. Barnes, S.R. Hirsch, Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia, J. Neurol. Neurosurg. Psychiatry 65 (1998) 446–453.
[99] H.J. Gertz, J. Cervos-Navarro, V. Ewald, The septo–hippocampal pathway in patients suffering from senile dementia of Alzheimer's type. Evidence for neuronal plasticity?, Neurosci. Lett. 76 (1987) 228–232.
[100] Y. Gilgun-Sherki, E. Melamed, D. Offen, Oxidative stress induced-neurodegenerative diseases: the need for antioxidants that penetrate the blood brain barrier, Neuropharmacology 40 (2001) 959–975.
[101] L.A. Glantz, D.A. Lewis, Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia, Arch. Gen. Psychiatry 57 (2000) 65–73.
[102] A. Globus, Brain morphology as a function of presynaptic morphology and activity, in: H. Reisen (Ed.), Developmental Neuropsychology of Sensory Deprivation, Academic Press, New York, 1975, pp. 9–91.
[103] A. Globus, M.R. Rosenzweig, E.L. Bennett, M.C. Diamond, Effects of differential experience on dendritic spine counts in rat cerebral cortex, J. Comp. Physiol. Psychol. 82 (1973) 175–181.

[104] A. Globus, A.B. Scheibel, Synaptic loci on parietal cortical neurons: terminations of the corpus callosum fibers, Science 156 (1967) 1127–1129.
[105] A. Globus, A.B. Scheibel, The effect of visual deprivation on cortical neurons: a Golgi study, Exp. Neurol. 19 (1967) 331–345.
[106] E. Gould, M.D. Allan, B.S. McEwen, Dendritic spine density of adult hippocampal pyramidal cells is sensitive to thyroid hormone, Brain Res. 525 (1990) 327–329.
[107] E.G. Gray, Electron microscopy of synaptic contacts on dendritic spines of the cerebral cortex, Nature 183 (1959) 1592–1593.
[108] P. Guidetti, V. Charles, E.Y. Chen, P.H. Reddy, J.H. Kordower, W.O. Whetsell Jr., R. Schwarcz, D.A. Tagle, Early degenerative changes in transgenic mice expressing mutant huntingtin involve dendritic abnormalities but no impairment of mitochondrial energy production, Exp. Neurol. 169 (2001) 340–350.
[109] G. Halliday, K. Cullen, A. Harding, Neuropathological correlates of memory dysfunction in the Wernicke–Korsakoff syndrome, Alcohol Alcohol. Suppl. 2 (1994) 245–251.
[110] S. Halpain, A. Hipolito, L. Saffer, Regulation of F-actin stability in dendritic spines by glutamate receptors and calcineurin, J. Neurosci. 18 (1998) 9835–9844.
[111] K.M. Harris, Structure, development, and plasticity of dendritic spines, Curr. Opin. Neurobiol. 9 (1999) 343–348.
[112] K.M. Harris, F.E. Jensen, B. Tsao, Three-dimensional structure of dendritic spines and synapses in rat hippocampus (CA1) at postnatal day 15 and adult ages: implications for the maturation of synaptic physiology and long-term potentiation, J. Neurosci. 12 (1992) 2685–2705.
[113] K.M. Harris, S.B. Kater, Dendritic spines: cellular specializations imparting both stability and flexibility to synaptic function, Annu. Rev. Neurosci. 17 (1994) 341–371.
[114] K.M. Harris, J.K. Stevens, Dendritic spines of rat cerebellar Purkinje cells: serial electron microscopy with reference to their biophysical characteristics, J. Neurosci. 8 (1988) 4455–4469.
[115] K.M. Harris, J.K. Stevens, Dendritic spines of CA1 pyramidal cells in the rat hippocampus: serial electron microscopy with reference to their biophysical characteristics, J. Neurosci. 9 (1989) 2982–2997.
[116] K.M. Harris, P. Sultan, Variation in the number, location, and size of synaptic vesicles provides an anatomical basis for the nonuniform probability of release at hippocampal CA1 synapses, Neuropharmacology 34 (1995) 1387–1395.
[117] M.J. Hasbani, M.L. Schlief, D.A. Fisher, M.P. Goldberg, Dendritic spines lost during glutamate receptor activation reemerge at original sites of synaptic contact, J. Neurosci. 21 (2001) 2393–2403.
[118] Y. Higashi, S. Murayama, P.G. Pentchev, K. Suzuki, Cerebellar degeneration in the Niemann–Pick type C mouse, Acta Neuropathol. (Berlin) 85 (1993) 175–184.
[119] D.E. Hillman, S. Chen, Vulnerability of cerebellar development in malnutrition—I. Quantitation of layer volume and neuron numbers, Neuroscience 6 (1981) 1249–1262.
[120] V.J. Hinton, W.T. Brown, K. Wisniewski, R.D. Rudelli, Analysis of neocortex in three males with the fragile X syndrome, Am. J. Med. Genet. 41 (1991) 289–294.
[121] A. Hirano, J.F. Llena, J.H. French, N.R. Ghatak, Fine structure of the cerebellar cortex in Menkes Kinky-hair disease. X-chromosome-linked copper malabsorption, Arch. Neurol. 34 (1977) 52–56.
[122] A. Hirano, The normal and aberrant development of synaptic structures between parallel fibers and Purkinje cell dendritic spines, J. Neural Trans. Suppl. 18 (1983) 1–8.
[123] R.N. Hogan, J.R. Baringer, S.B. Prusiner, Scrapie infection diminishes spines and increases varicosities of dendrites in hamsters: a quantitative Golgi analysis, J. Neuropathol. Exp. Neurol. 46 (1987) 461–473.
[124] C.H. Horner, Plasticity of the dendritic spine, Prog. Neurobiol. 41 (1993) 281–321.
[125] P.R. Huttenlocher, Dendritic development and mental defect, Neurology 20 (1970) 381.
[126] P.R. Huttenlocher, Dendritic and synaptic pathology in mental retardation, Pediatr. Neurol. 7 (1991) 79–85.
[127] P.R. Huttenlocher, A.S. Dabholkar, Regional differences in synaptogenesis in human cerebral cortex, J. Comp. Neurol. 387 (1997) 167–178.
[128] C.A. Ingham, S.H. Hood, G.W. Arbuthnott, Spine density on neostriatal neurones changes with 6-hydroxydopamine lesions and with age, Brain Res. 503 (1989) 334–338.
[129] C.A. Ingham, S.H. Hood, P. Taggart, G.W. Arbuthnott, Plasticity of synapses in the rat neostriatum after unilateral lesion of the nigrostriatal dopaminergic pathway, J. Neurosci. 18 (1998) 4732–4743.
[130] S.A. Irwin, B. Patel, M. Idupulapati, J.B. Harris, R.A. Crisostomo, B.P. Larsen, F. Kooy, P.J. Willems, P. Cras, P.B. Kozlowski, R.A. Swain, I.J. Weiler, W.T. Greenough, Abnormal dendritic spine characteristics in the temporal and visual cortices of patients with fragile-X syndrome: a quantitative examination, Am. J. Med. Genet. 98 (2001) 161–167.
[131] M. Isokawa, Remodeling dendritic spines of dentate granule cells in temporal lobe epilepsy patients and the rat pilocarpine model, Epilepsia 41 (Suppl. 6) (2000) S14–17.
[132] V. Jay, L.E. Becker, F.W. Chan, T.L. Perry Sr., Puppet-like syndrome of Angelman: a pathologic and neurochemical study, Neurology 41 (1991) 416–422.
[133] M. Jeffrey, W.G. Halliday, C.M. Goodsir, A morphometric and immunohistochemical study of the vestibular nuclear complex in bovine spongiform encephalopathy, Acta Neuropathol. (Berlin) 84 (1992) 651–657.
[134] M. Jiang, C.L. Lee, K.L. Smith, J.W. Swann, Spine loss and other persistent alterations of hippocampal pyramidal cell dendrites in a model of early-onset epilepsy, J. Neurosci. 18 (1998) 8356–8368.
[135] A.R. Johnston, C. Black, J. Fraser, N. MacLeod, Scrapie infection alters the membrane and synaptic properties of mouse hippocampal CA1 pyramidal neurones, J. Physiol. 500 (1997) 1–15.
[136] A. Kamei, S. Takashima, F. Chan, L.E. Becker, Abnormal dendritic development in maple syrup urine disease, Pediatr. Neurol. 8 (1992) 145–147.
[137] W.E. Kaufmann, H.W. Moser, Dendritic anomalies in disorders associated with mental retardation, Cereb. Cortex 10 (2000) 981–991.
[138] J.J. Kelley, X.M. Gao, C.A. Tamminga, R.C. Roberts, The effect of chronic haloperidol treatment on dendritic spines in the rat striatum, Exp. Neurol. 146 (1997) 471–478.
[139] L. Kilham, G. Margolis, Viral etiology of spontaneous ataxia in cats, Am. J. Pathol. 48 (1966) 991–1011.
[140] J.H. Kim, E.E. Manuelidis, Neuronal alterations in experimental Creutzfeldt–Jakob disease: a Golgi study, J. Neurol. Sci. 89 (1989) 93–101.
[141] H.C. Kinney, D.D. Armstrong, Perinatal neuropathology, in: D.I. Graham, P.L. Lanton (Eds.), Greenfield's Neuropathology, Oxford University Press, New York, 1997, pp. 535–599.
[142] E. Király, D.G. Jones, Dendritic spine changes in rat hippocampal pyramidal cells after postnatal lead treatment: a Golgi study, Exp. Neurol. 77 (1982) 236–239.
[143] S.A. Kirov, K.M. Harris, Dendrites are more spiny on mature hippocampal neurons when synapses are inactivated, Nat. Neurosci. 2 (1999) 878–883.
[144] T. Kuge, T. Asayama, S. Kakuta, K. Murakami, Y. Ishikawa, M. Kuroda, T. Imai, K. Seki, M. Omoto, K. Kishi, Effect of ethanol on the development and maturation of synapses in the rat hippocampus: a quantitative electron-microscope study, Environ. Res. 62 (1993) 99–105.
[145] D.J. Lacey, Cortical dendritic spine loss in rat pups whose mothers were prenatally injected with phenylacetate ('maternal PKU' model), Brain Res. 27 (1986) 283–285.

[146] D.J. Lacey, Normalization of dendritic spine numbers in rat hippocampus after termination of phenylacetate injections (PKU model), Brain Res. 329 (1985) 354–355.
[147] D.J. Lacey, K. Terplan, Abnormal cerebral cortical neurons in a child with maternal PKU syndrome, J. Child Neurol. 2 (1987) 201–204.
[148] M. Lafarga, M.T. Berciano, I. Saurez, M.A. Andres, J. Berciano, Reactive astroglia–neuron relationships in the human cerebellar cortex: a quantitative, morphological and immunocytochemical study in Creutzfeldt–Jakob disease, Int. J. Dev. Neurosci. 11 (1993) 199–213.
[149] L.M.H. Larramendi, Analysis of synaptogenesis in the cerebellum of the mouse, in: R.R. Llinas (Ed.), The Neurobiology of Cerebellar Evolution and Development, AMA, Chicago, IL, 1969, pp. 803–843.
[150] H. Lassmann, Patterns of synaptic and nerve cell pathology in Alzheimer's disease, Behav. Brain Res. 78 (1996) 9–14.
[151] J.M. Lauder, Thyroid influences on the developing cerebellum and hippocampus of the rat, in: G.R. Delong, J. Robbins, P.G. Condliffe (Eds.), Iodine and the Brain, Plenum Press, New York, 1989, pp. 79–90.
[152] B. Lendvai, E.A. Stern, B. Chen, K. Svoboda, Experience-dependent plasticity of dendritic spines in the developing rat barrel cortex in vivo, Nature 404 (2000) 876–881.
[153] L. Lescaudron, A. Verna, Effects of chronic ethanol consumption on pyramidal neurons of the mouse dorsal and ventral hippocampus: a quantitative histological analysis, Exp. Brain Res. 58 (1985) 362–367.
[154] L. Lescaudron, R. Jaffard, A. Verna, Modifications in number and morphology of dendritic spines resulting from chronic ethanol consumption and withdrawal: a Golgi study in the mouse anterior and posterior hippocampus, Exp. Neurol. 106 (1989) 156–163.
[155] G. Leuba, T. Rabinowicz, Long-term effects of postnatal undernutrition and maternal malnutrition on mouse cerebral cortex. II. Evolution of dendritic branchings and spines in the visual region, Exp. Brain Res. 37 (1979) 299–308.
[156] Z. Liposits, I. Kallo, E. Hrabovszky, F. Gallyas, Ultrastructural pathology of degenerating 'dark' granule cells in the hippocampal dentate gyrus of adrenalectomized rats, Acta Biol. Hung. 48 (1997) 173–187.
[157] P. Lipton, Ischemic cell death in brain neurons, Physiol. Rev. 79 (1999) 1431–1586.
[158] R. Llinas, D.E. Hillman, W. Precht, Neuronal circuit reorganization in mammalian agranular cerebellar cortex, J. Neurobiol. 4 (1973) 69–94.
[159] D. Lopez-Tejero, I. Ferrer, M. Llobera, E. Herrera, Effects of prenatal ethanol exposure on physical growth, sensory reflex maturation and brain development in the rat, Neuropathol. Appl. Neurobiol. 12 (1986) 251–260.
[160] D. Lorton, W.J. Anderson, The effects of postnatal lead toxicity on the development of cerebellum in rats, Neurobehav. Toxicol. Teratol. 8 (1986) 51–59.
[161] N.V. Lukoyanov, J.P. Andrade, Behavioral effects of protein deprivation and rehabilitation in adult rats: relevance to morphological alterations in the hippocampal formation, Behav. Brain Res. 112 (2000) 85–97.
[162] J. Luo, M.W. Miller, Growth factor-mediated neural proliferation: target of ethanol toxicity, Brain Res. Brain Res. Rev. 27 (1998) 157–167.
[163] J.S. Lund, S.M. Holbach, W.W. Chung, Postnatal development of thalamic recipient neurons in the monkey striate cortex: II. Influence of afferent driving on spine acquisition and dendritic growth of layer 4C spiny stellate neurons, J. Comp. Neurol. 309 (1991) 129–140.
[164] J.P. Machado-Salas, Abnormal dendritic patterns and aberrant spine development in Bourneville's disease—a Golgi survey, Clin. Neuropathol. 3 (1984) 52–58.
[165] M.D. Madeira, A. Pereira, A. Cadete-Leite, M.M. Paula-Barbosa, Estimates of volumes and pyramidal cell numbers in the prelimbic subarea of the prefrontal cortex in experimental hypothyroid rats, J. Anat. 171 (1990) 41–56.
[166] A.M. Magarinos, B.S. McEwen, Stress-induced atrophy of apical dendrites of hippocampal CA3c neurons: comparison of stressors, Neuroscience 69 (1995) 83–88.
[167] S.E. Maier, J.A. Miller, J.M. Blackwell, J.R. West, Fetal alcohol exposure and temporal vulnerability: regional differences in cell loss as a function of the timing of binge-like alcohol exposure during brain development, Alcohol. Clin. Exp. Res. 23 (1999) 726–734.
[168] J. Mariani, F. Crepel, K. Mikoshiba, J.P. Changeux, C. Sotelo, Anatomical, physiological and biochemical studies of the cerebellum from reeler mutant mouse, Phil. Trans. R. Soc. Ser. B 281 (1977) 1–28.
[169] M. Marin-Padilla, Structural abnormalities of the cerebral cortex in human chromosomal aberrations: a Golgi study, Brain Res. 44 (1972) 625–629.
[170] M. Marin-Padilla, Structural organization of the cerebral cortex (motor area) in human chromosomal abberations. A Golgi study. I. D1 (13–15) trisomy, Patau syndrome, Brain Res. 60 (1974) 375–391.
[171] M. Marin-Padilla, Pyramidal cell abnormalities in the motor cortex of a child with Down's syndrome. A Golgi study, J. Comp. Neurol. 167 (1976) 63–81.
[172] L.J. Martin, N.A. Al-Abdulla, A.M. Brambrink, J.R. Kirsch, F.E. Sieber, C. Portera-Cailliau, Neurodegeneration in excitotoxicity, global cerebral ischemia, and target deprivation: a perspective on the contributions of apoptosis and necrosis, Brain Res. Bull. 46 (1998) 281–309.
[173] M.E. Martone, B.R. Hu, M.H. Ellisman, Alterations of hippocampal postsynaptic densities following transient ischemia, Hippocampus 10 (2000) 610–616.
[174] M.E. Martone, H. Zhang, V.M. Simpliciano, B.O. Carragher, M.H. Ellisman, Three-dimensional visualization of the smooth endoplasmic reticulum in Purkinje cell dendrites, J. Neurosci. 13 (1993) 4636–4646.
[175] E. Masliah, N. Ge, M. Morey, R. DeTeresa, R.D. Terry, C.A. Wiley, Cortical dendritic pathology in human immunodeficiency virus encephalitis, Lab. Invest. 66 (1992) 285–291.
[176] D.E. Matthews, C. Cotman, G. Lynch, An electron microscopic study of lesion-induced synaptogenesis in the dentate gyrus of the adult rat. I. Magnitude and time–course of degeneration, Brain Res. 115 (1976) 1–21.
[177] A. Matus, Actin-based plasticity in dendritic spines, Science 290 (2000) 754–758.
[178] J.P. McAllister II, T.A. Maugans, M.V. Shah, R.C. Truex Jr., Neuronal effects of experimentally induced hydrocephalus in newborn rats, J. Neurosurg. 63 (1985) 776–783.
[179] N.T. McMullen, E.M. Glaser, Auditory cortical responses to neonatal deafening: pyramidal neuron spine loss without changes in growth or orientation, Exp. Brain Res. 72 (1988) 195–200.
[180] D.L. McNeill, K. Chung, C.E. Hulsebosch, R.P. Bolender, R.E. Coggeshall, Numbers of synapses in laminae I–IV of the rat dorsal horn, J. Comp. Neurol. 278 (1988) 453–460.
[181] T.H. McNeill, S.A. Brown, J.A. Rafols, I. Shoulson, Atrophy of medium spiny I striatal dendrites in advanced Parkinson's disease, Brain Res. 455 (1988) 148–152.
[182] R. McWilliams, G. Lynch, Terminal proliferation and synaptogenesis following partial deafferentation: the reinnervation of the inner molecular layer of the dentate gyrus following removal of its commissural afferents, J. Comp. Neurol. 180 (1978) 581–616.
[183] M.W. Miller, G. Potempa, Numbers of neurons and glia in mature rat somatosensory cortex: effects of prenatal exposure to ethanol, J. Comp. Neurol. 293 (1990) 92–102.
[184] S.A. Mohamed, E.J. Nathaniel, D.R. Nathaniel, L. Snell, Altered

Purkinje cell maturation in rats exposed prenatally to ethanol. II. Synaptology, Exp. Neurol. 97 (1987) 53–69.
[185] M.M. Montgomery, A.F. Dean, F. Taffs, E.J. Stott, P.L. Lantos, P.J. Luthert, Progressive dendritic pathology in cynomolgus macaques infected with simian immunodeficiency virus, Neuropathol. Appl. Neurobiol. 25 (1999) 11–19.
[186] A.M. Mouren-Mathieu, M. Colonnier, The molecular layer of the adult cat cerebellar cortex after lesion of the parallel fibers: an optic and electron microscope study, Brain Res. 16 (1969) 307–323.
[187] W. Muller, J.A. Conner, Dendritic spines as individual neuronal compartments for synaptic $Ca^{2+}$ responses, Nature 354 (1991) 73–76.
[188] M. Muller, B.H. Gahwiler, L. Rietschin, S.M. Thompson, Reversible loss of dendritic spines and altered excitability after chronic epilepsy in hippocampal slice cultures, Proc. Natl. Acad. Sci. USA 90 (1993) 257–261.
[189] J.A. Munoz-Cueto, L.M. Garcia-Segura, A. Ruiz-Marcos, Developmental sex differences and effect of ovariectomy on the number of cortical pyramidal cell dendritic spines, Brain Res. 515 (1990) 64–68.
[190] R.M. Nagra, E. Masliah, P.G. Burrola, C.A. Wiley, Neocortical pathology in chronic murine retroviral encephalitis, J. Neuropathol. Exp. Neurol. 53 (1994) 572–581.
[191] R. Nau, W. Brück, Neuronal injury in bacterial meningitis: mechanisms and implications for therapy, Trends Neurosci. 25 (2002) 38–45.
[192] E.A. Nimchinsky, A.M. Oberlander, K. Svoboda, Abnormal development of dendritic spines in FMR1 knock-out mice, J. Neurosci. 21 (2001) 5139–5146.
[193] S. Norton, B. Culver, A Golgi analysis of caudate neurons in rats exposed to carbon monoxide, Brain Res. 132 (1977) 455–465.
[194] M.J. Obregon, P. Santisteban, A. Rodriguez-Pena, A. Pascual, P. Cartagena, A. Ruiz-Marcos, L. Lamas, F. Escobar del Rey, G. Morreale de Escobar, Cerebral hypothyroidism in rats with adult-onset iodine deficiency, Endocrinology 115 (1984) 614–624.
[195] M.M. Okazaki, D.A. Evenson, J.V. Nadler, Hippocampal mossy fiber sprouting and synapse formation after status epilepticus in rats: visualization after retrograde transport of biocytin, J. Comp. Neurol. 352 (1995) 515–534.
[196] J. O'Kusky, Synaptic degeneration in rat visual cortex after neonatal administration of methylmercury, Exp. Neurol. 89 (1985) 32–47.
[197] J.R. O'Kusky, M.G. Norman, Sudden infant death syndrome: increased synaptic density in the central reticular nucleus of the medulla, J. Neuropathol. Exp. Neurol. 53 (1994) 263–271.
[198] J.S. Park, M.C. Bateman, M.P. Goldberg, Rapid alterations in dendrite morphology during sublethal hypoxia or glutamate receptor activation, Neurobiol. Dis. 3 (1996) 215–227.
[199] J.G. Parnavelas, G. Lynch, N. Brecha, C.W. Cotman, A. Globus, Spine loss and regrowth in hippocampus following deafferentation, Nature 248 (1974) 71–73.
[200] G.W. Patrick, W.J. Anderson, Dendritic alterations of cortical pyramidal neurons in postnatally lead-exposed kittens: a Golgi–Cox study, Dev. Neurosci. 17 (1995) 219–229.
[201] G.W. Patrick, W.J. Anderson, Dendritic alterations of cerebellar Purkinje neurons in postnatally lead-exposed kittens, Dev. Neurosci. 22 (2000) 320–328.
[202] S. Patt, L.A. Gerhard, Golgi study of human locus coeruleus in normal brains and in Parkinson's disease, Neuropathol. Appl. Neurobiol. 19 (1993) 519–523.
[203] S. Patt, H.J. Gertz, L. Gerhard, J. Cervos-Navarro, Pathological changes in dendrites of substantia nigra neurons in Parkinson's disease: a Golgi study, Histol. Histopathol. 6 (1991) 373–380.
[204] M.G. Paule, A.S. Rowland, S.A. Ferguson, J.J. Chelonis, R. Tannock, J.M. Swanson, F.X. Castellanos, Attention deficit/hyperactivity disorder: characteristics, interventions, and models, Neurotoxicol. Teratol. 22 (2000) 631–651.
[205] D.P. Perl, Abnormalities in brain structure on postmortem analysis of dementias, in: D.S. Charney, E.J. Nestler, B.S. Bunney (Eds.), Neurobiology of Mental Illness, Oxford University Press, New York, 1999, pp. 715–722.
[206] A. Peters, I.R. Kaiserman-Abramof, The small pyramidal neuron of the rat cerebral cortex. The synapses upon dendritic spines, Z. Zellforsch. Mikrosk. Anat. 100 (1969) 487–506.
[207] A. Peters, C. Sethares, M.B. Moss, The effects of aging on layer I in area 46 of prefrontal cortex in the rhesus monkey, Cereb. Cortex 8 (1998) 671–684.
[208] J. Pokorny, S. Trojan, J. Fischer, Changes in the structure of the rat hippocampus after prolonged postnatal hypoxia, Physiol. Bohemoslov 31 (1982) 193–202.
[209] J.T. Povlishock, Traumatically induced axonal injury: pathogenesis and pathobiological implications, Brain Pathol. 2 (1992) 1–12.
[210] C. Power, Retroviral diseases of the nervous system: pathogenic host response or viral gene-mediated neurovirulence?, Trends Neurosci. 24 (2001) 162–169.
[211] D.P. Purpura, Dendritic spine 'dysgenesis' and mental retardation, Science 186 (1974) 1126–1128.
[212] D.P. Purpura, N. Bodick, K. Suzuki, I. Rapin, S. Wurzelmann, Microtubule disarray in cortical dendrites and neurobehavioral failure. I. Golgi and electron microscopic studies, Dev. Brain. Res. 5 (1982) 287–297.
[213] J.J. Quattrochi, P.T. McBride, A.J. Yates, Brainstem immaturity in sudden infant death syndrome: a quantitative rapid Golgi study of dendritic spines in 95 infants, Brain Res. 325 (1985) 39–48.
[214] G. Raisman, P.M. Field, A quantitative investigation of the development of collateral reinnervation after partial deafferentation of the septal nuclei, Brain Res. 50 (1973) 241–264.
[215] P. Rakic, R.L. Sidman, Organization of cerebellar cortex secondary to deficit of granule cells in weaver mutant mice, J. Comp. Neurol. 152 (1973) 133–162.
[216] G.J.A. Ramakers, Rho proteins and the cellular mechanisms of mental retardation, Am. J. Med. Genet. 94 (2000) 367–371.
[217] T. Ramakrishna, Vitamins and brain development, Physiol. Res. 48 (1999) 175–187.
[218] S. Ramón y Cajal, Histology of the Nervous System of Man and Vertebrates, Oxford University Press, New York, 1995, Translated by N. Swanson and L.W. Swanson.
[219] S. Ramón y Cajal, Cajal's Degeneration and Regeneration of the Nervous System, Oxford University Press, New York, 1991, Translated by R.M. May, Edited with an Introduction and Additional Translations by J. DeFelipe and E.G. Jones.
[220] S. Rees, S. Breen, M. Loeliger, G. McCrabb, R. Harding, Hypoxemia near mid-gestation has long-term effects on fetal brain development, J. Neuropathol. Exp. Neurol. 58 (1999) 932–945.
[221] W.O. Renier, F.J. Gabreels, H.H. Jaspar, Morphological and biochemical analysis of a brain biopsy in a case of idiopathic Lennox–Gastaut syndrome, Epilepsia 29 (1988) 644–649.
[222] A. Represa, I. Jorquera, G. Le Gal La Salle, Y. Ben-Ari, Epilepsy induced collateral sprouting of hippocampal mossy fibers: does it induce the development of ectopic synapses with granule cell dendrites?, Hippocampus 3 (1993) 257–268.
[223] R.C. Roberts, R. Conley, L. Kung, F.J. Peretti, D.J. Chute, Reduced striatal spine size in schizophrenia: a postmortem ultrastructural study, Neuroreport 7 (1996) 1214–1218.
[224] T.E. Robinson, B. Kolb, Alterations in the morphology of dendrites and dendritic spines in the nucleus accumbens and prefrontal cortex following repeated treatment with amphetamine or cocaine, Eur. J. Neurosci. 11 (1999) 1598–1604.
[225] T.E. Robinson, B. Kolb, Morphine alters the structure of neurons in the nucleus accumbens and neocortex of rats, Synapse 33 (1999) 160–162.
[226] A. Ruiz-Marcos, Quantitative studies of the effects of hypothyroidism on the development of the cerebral cortex, in: G.R. Delong, J. Robbins, P.G. Condliffe (Eds.), Iodine and the Brain, Plenum Press, New York, 1989, pp. 91–102.

[227] A. Ruiz-Marcos, F. Sanchez-Toscano, F. Escobar del Rey, G. Morreale de Escobar, Severe hypothyroidism and the maturation of the rat cerebral cortex, Brain Res. 162 (1979) 315–329.
[228] A. Ruiz-Marcos, F. Sanchez-Toscano, F. Escobar del Rey, G. Morreale de Escobar, Reversible morphological alterations of cortical neurons in juvenile and adult hypothyroidism in the rat, Brain Res. 185 (1980) 91–102.
[229] A. Ruiz-Marcos, F. Sanchez-Toscano, M.J. Obregon, F. Escobar del Rey, G. Morreale de Escobar, Thyroxine treatment and recovery of hypothyroidism-induced pyramidal cell damage, Brain Res. 239 (1982) 559–574.
[230] L.T. Rutledge, J. Duncan, N. Cant, Long-term status of pyramidal cell axon collaterals and apical dendritic spines in denervated cortex, Brain Res. 41 (1972) 249–262.
[231] B. Sakic, H. Szechtman, J.A. Denburg, G. Gorny, B. Kolb, I.Q. Whishaw, Progressive atrophy of pyramidal neuron dendrites in autoimmune MRL-lpr mice, J. Neuroimmunol. 87 (1998) 162–170.
[232] R.M. Sapolsky, Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders, Arch. Gen. Psychiatry 57 (2000) 925–935.
[233] M.B. Schapiro, N.P. Rosman, T.L. Kemper, Effects of chronic exposure to alcohol on the developing brain, Neurobehav. Toxicol. Teratol. 6 (1984) 351–356.
[234] S.W. Scheff, S.T. DeKosky, D.A. Price, Quantitative assessment of cortical synaptic density in Alzheimer's disease, Neurobiol. Aging 11 (1990) 29–37.
[235] S.W. Scheff, D.A. Price, Synapse loss in the temporal lobe in Alzheimer's disease, Ann. Neurol. 33 (1993) 190–199.
[236] A.B. Scheibel, The hippocampus: organizational patterns in health and senescence, Mech. Ageing Dev. 9 (1979) 89–102.
[237] A.B. Scheibel, Dendritic changes, in: B. Reisberg (Ed.), Alzheimer's Disease, The Free Press, New York, 1983, pp. 69–73.
[238] M.E. Scheibel, A.B. Scheibel, On the nature of dendritic spines—report of a workshop, Commun. Behav. Biol., Part A 1 (1968) 231–265.
[239] M.E. Scheibel, A.B. Scheibel, Specific postnatal threats to brain development: dendritic changes, in: S.R. Berenberg (Ed.), Brain: Fetal and Infant: Current Research on Normal and Abnormal Development, Martinus Nijhoff Medical Division, The Hague, 1977, pp. 302–315.
[240] T. Schikorski, C.F. Stevens, Quantitative fine-structural analysis of olfactory cortical synapses, Proc. Natl. Acad. Sci. USA 96 (1999) 4107–4112.
[241] B. Schönheit, P. Haensel, Effect of nonspecific malnutrition on spine morphology of lamina V pyramidal cells of the cingulate area of juvenile and adult rats, J. Hirnforsch. 25 (1984) 617–631.
[242] T.J. Shors, C. Chua, J. Falduto, Sex differences and opposite effects of stress on dendritic spine density in the male versus female hippocampus, J. Neurosci. 21 (2001) 6292–6297.
[243] M. Segal, Dendritic spines for neuroprotection: a hypothesis, Trends Neurosci. 18 (1995) 468–471.
[244] G.M. Shepherd, The dendritic spine: a multifunctional integrative unit, J. Neurophysiol. 75 (1996) 2197–2210.
[245] G.M.G. Shepherd, K.M. Harris, Three-dimensional structure and composition of CA3→CA1 axons in rat hippocampal slices: implications for presynaptic connectivity and compartmentalization, J. Neurosci. 18 (1998) 8300–8310.
[246] B.T. Sherwin, S. Jacobson, S.L. Troxell, A.E. Rogers, R.W. Pelham, A rat model (using a semipurified diet) of the fetal alcohol syndrome, Curr. Alcohol 7 (1979) 15–30.
[247] K.E. Sorra, K.M. Harris, Occurrence and three-dimensional structure of multiple synapses between individual radiatum axons and their target pyramidal cells in hippocampal area CA1, J. Neurosci. 13 (1993) 3736–3748.
[248] C. Sotelo, Permanence and fate of paramembranous synaptic specialization in 'mutant' and experimental animals, Brain Res. 62 (1973) 345–351.
[249] C. Sotelo, Formation of presynaptic dendrites in the rat cerebellum following neonatal x-irradiation, Neuroscience 2 (1977) 275–283.
[250] C. Sotelo, Cerebellar synaptogenesis: what we can learn from mutant mice, J. Exp. Biol. 153 (1990) 225–249.
[251] C. Sotelo, D.E. Hillman, A.K. Zamora, R. Llinas, Climbing fibre deafferentation: its action on Purkinje cell dendritic spines, Brain Res. 98 (1975) 574–581.
[252] A. Sotrel, R.S. Williams, W.E. Kaufmann, R.H. Myers, Evidence for neuronal degeneration and dendritic plasticity in cortical pyramidal neurons of Huntington's disease: a quantitative Golgi study, Neurology 43 (1993) 2088–2096.
[253] N. Sousa, N.V. Lukoyanov, M.D. Madeira, O.F. Almeida, M.M. Paula-Barbosa, Reorganization of the morphology of hippocampal neurites and synapses after stress-induced damage correlates with behavioral improvement, Neuroscience 97 (2000) 253–266.
[254] N. Sousa, M.D. Madeira, M.M. Paula-Barbosa, Corticosterone replacement restores normal morphological features to the hippocampal dendrites, axons and synapses of adrenalectomized rats, J. Neurocytol. 28 (1999) 541–558.
[255] J. Spacek, 'Free' postsynaptic-like densities in normal adult brain: their occurrence,distribution, structure and association with subsurface cisterns, J. Neurocytol. 11 (1982) 693–706.
[256] J. Spacek, Three-dimensional analysis of dendritic spines. II. Spine apparatus and other cytoplasmic components, Anat. Embryol. 171 (1985) 235–243.
[257] J. Spacek, Ultrastructural pathology of dendritic spines in epitumorous human cerebral cortex, Acta Neuropathol. (Berlin) 73 (1987) 77–85.
[258] J. Spacek, K.M. Harris, Three-dimensional organization of smooth endoplasmic reticulum in hippocampal CA1 dendrites and dendritic spines of the immature and mature rat, J. Neurosci. 17 (1997) 190–203.
[259] J. Spacek, M. Hartmann, Three-dimensional analysis of dendritic spines. I. Quantitative observations related to dendritic spine and synaptic morphology in cerebral and cerebellar cortices, Anat. Embryol. 167 (1983) 289–310.
[260] O. Steward, Alterations in polyribosomes associated with dendritic spines during reinnervation of the detate gyrus of the adult rat, J. Neurosci. 3 (1983) 177–188.
[261] O. Steward, W.B. Levy, Preferential localization of polyribosomes under the base of dendritic spines in granule cells of the dentate gyrus, J. Neurosci. 2 (1982) 284–291.
[262] O. Steward, S.L. Vinsant, L. Davis, The process of reinnervation in the dentate gyrus of adult rats: an ultrastructural study of changes in presynaptic terminals as a result of sprouting, J. Comp. Neurol. 267 (1988) 203–210.
[263] G. Stoltenburg-Didinger, S. Markwort, Prenatal methylmercury exposure results in dendritic spine dysgenesis in rats, Neurotoxicol. Teratol. 12 (1990) 573–576.
[264] G. Stoltenburg-Didinger, H.L. Spohr, Fetal alcohol syndrome and mental retardation: spine distribution of pyramidal cells in prenatal alcohol-exposed rat cerebral cortex; a Golgi study, Brain Res. 313 (1983) 119–123.
[265] M. Suetsugu, P. Mehraein, Spine distribution along the apical dendrites of the pyramidal neurons in Down's syndrome. A quantitative Golgi study, Acta Neuropathol. (Berlin) 50 (1980) 207–210.
[266] M.S. Sunanda Rao, T.R. Raju, Effect of chronic restraint stress on dendritic spines and excrescences of hippocampal CA3 neurons—a quantitative study, Brain Res. 694 (1995) 312–317.
[267] N.V. Swindale, Dendritic spines only connect, Trends Neurosci. 4 (1981) 240–241.
[268] S. Takashima, T. Mito, H. Yamanouchi, Developmental brain-stem pathology in sudden infant death syndrome, Acta Paediatr. Japan 36 (1994) 317–320.
[269] S. Takashima, L.E. Becker, Developmental abnormalities of medullary 'respiratory centers' in sudden infant death syndrome, Exp. Neurol. 90 (1985) 580–587.

[270] S. Takashima, L.E. Becker, Delayed dendritic development of catecholaminergic neurons in the ventrolateral medulla of children who died of sudden infant death syndrome, Neuropediatrics 22 (1991) 97–99.
[271] S. Takashima, L.E. Becker, D.L. Armstrong, F.-W. Chan, Abnormal neuronal development in the visual cortex of the human fetus and infant with Down's syndrome. A quantitative and qualitative Golgi study, Brain Res. 225 (1981) 1–21.
[272] S. Takashima, F. Chan, L.E. Becker, Cortical dysgenesis in a variant of phenylketonuria (dihydropteridine reductase deficiency), Pediatr. Pathol. 11 (1991) 771–779.
[273] S. Takashima, K. Iida, T. Mito, M. Arima, Dendritic and histochemical development and ageing in patients with Down's syndrome, J. Intellect. Disabil. Res. 38 (1994) 265–273.
[274] M.A. Tavares, M.M. Paula-Barbosa, E.G. Gray, Dendritic spine plasticity and chronic alcoholism in rats, Neurosci. Lett. 42 (1983) 235–238.
[275] J.D. Thomas, C.R. Goodlett, J.R. West, Alcohol-induced Purkinje cell loss depends on developmental timing of alcohol exposure and correlates with motor performance, Brain Res. Dev. Brain Res. 105 (1998) 159–166.
[276] S.M. Thompson, C. Fortunato, R.A. McKinney, M. Muller, B.H. Gahwiler, Mechanisms underlying the neuropathological consequences of epileptic activity in the rat hippocampus in vitro, J. Comp. Neurol. 372 (1996) 515–528.
[277] S.B. Tieman, The anatomy of geniculocortical connections in monocularly deprived cats, Cell. Mol. Neurobiol. 5 (1985) 35–45.
[278] K.G. Todd, R.F. Butterworth, Mechanisms of selective neuronal cell death due to thiamine deficiency, Ann. N.Y. Acad. Sci. 893 (1999) 404–411.
[279] G.P. Toth, R.E. Long, T.S. Mills, M.K. Smith, Effects of chlorine dioxide on the developing rat brain, J. Toxicol. Environ. Health 31 (1990) 29–44.
[280] G.F. Tseng, M.E. Hu, Axotomy induces retraction of the dendritic arbor of adult rat rubrospinal neurons, Acta Anat. 155 (1996) 184–193.
[281] G.G. Turrigiano, K.R. Leslie, N.S. Desai, L.C. Rutherford, S.B. Nelson, Activity-dependent scaling of quantal amplitude in neocortical neurons, Nature 391 (1998) 892–896.
[282] G.G. Turrigiano, S.B. Nelson, Hebb and homeostasis in neuronal plasticity, Curr. Opin. Neurobiol. 10 (2000) 358–364.
[283] A.M. Turner, W.T. Greenough, Differential rearing effects on rat visual cortex synapses. I. Synaptic and neuronal density and synapses per neuron, Brain Res. 329 (1985) 195–203.
[284] F. Valverde, Apical dendritic spines of the visual cortex and light deprivation in the mouse, Exp. Brain Res. 3 (1967) 337–352.
[285] D.W. Vaughan, C.J. Cahill, Long-term effects of callosal lesions in the auditory cortex of rats of different ages, Neurobiol. Aging 5 (1984) 175–182.
[286] M. Victor, Alcoholic dementia, Can. J. Neurol. Sci. 21 (1994) 88–99.
[287] J. Vincent, C. Legrand, A. Rabie, J. Legrand, Effects of thyroid hormone on synaptogenesis in the molecular layer of the developing rat cerebellum, J. Physiol. (Paris) 78 (1982) 729–738.
[288] D.W. Walker, B.E. Hunter, W.C. Abraham, Neuroanatomical and functional deficits subsequent to chronic ethanol administration in animals, Alcohol Clin. Exp. Res. 5 (1981) 267–282.
[289] S.U. Walkley, H.J. Baker, Sphingomyelin lipidosis in a cat: Golgi studies, Acta Neuropathol. (Berlin) 65 (1984) 138–144.
[290] S.U. Walkley, H.J. Baker, M.C. Rattazzi, Initiation and growth of ectopic neurites and meganeurites during postnatal cortical development in ganglioside storage disease, Brain Res. Dev. Brain Res. 51 (1990) 167–178.
[291] Y. Watanabe, E. Gould, B.S. McEwen, Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons, Brain Res. 588 (1992) 341–345.
[292] S. Wenisch, B. Fortmann, T. Steinmetz, A. Kriete, R. Leiser, I. Bitsch, 3-D confocal laser scanning microscopy used in morphometric analysis of rat Purkinje cell dendritic spines after chronic ethanol consumption, Anat. Histol. Embryol. 27 (1998) 393–397.
[293] S. Wenisch, B. Fortmann, T. Steinmetz, R. Leiser, I. Bitsch, Neuroprotective effects of thiamine-megadoses after long-term ethanol application in the rat brain. A structural investigation of hippocampal CA1 pyramidal and cerebellar Purkinje neurons, J. Hirnforsch. 37 (1996) 377–387.
[294] S. Wenisch, T. Steinmetz, B. Fortmann, R. Leiser, I. Bitsch, Can megadoses of thiamine prevent ethanol-induced damages of rat hippocampal CA1 pyramidal neurones?, Z. Ernahrungswiss. 35 (1996) 266–272.
[295] J. Wenzel, S. Otani, N.L. Desmond, W.B. Levy, Rapid development of somatic spines in stratum granulosum of the adult hippocampus in vitro, Brain Res. 656 (1994) 127–134.
[296] R.S. Williams, R.J. Ferrante, V.S. Caviness, The Golgi rapid method in clinical neuropathology: the morphologic consequences of suboptimal fixation, J. Neuropathol. Exp. Neurol. 37 (1978) 13–33.
[297] K.E. Wisniewski, S.M. Segan, C.M. Miezejeski, E.A. Sersen, R.D. Rudelli, The Fra(X) syndrome: neurological, electrophysiological, and neuropathological abnormalities, Am. J. Med. Genet. 38 (1991) 476–480.
[298] W.T. Wong, R.O.L. Wong, Changing specificity of neurotransmitter regulation of rapid dendritic remodeling during synaptogenesis, Nat. Neurosci. 4 (2001) 351–352.
[299] C.S. Woolley, B.S. McEwen, Estradiol mediates fluctuation in hippocampal synapse density during the estrus cycle in the adult rat, J. Neurosci. 12 (1992) 2549–2554.
[300] C.S. Woolley, B.S. McEwen, Roles of estradiol and progesterone in regulation of hippocampal dendritic spine density during the estrous cycle in the rat, J. Comp. Neurol. 336 (1993) 293–306.
[301] C.S. Woolley, E. Gould, M. Frankfurt, B.S. McEwen, Naturally occurring fluctuation in dendritic spine density on adult hippocampal pyramidal neurons, J. Neurosci. 10 (1990) 4035–4039.
[302] C.S. Woolley, E. Gould, B.S. McEwen, Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons, Brain Res. 531 (1990) 225–231.
[303] C.S. Woolley, H.J. Wenzel, P.A. Schwartzkroin, Estradiol increases the frequency of multiple synapse boutons in the hippocampal CA1 region of the adult female rat, J. Comp. Neurol. 373 (1996) 108–117.
[304] R. Yuste, A. Majewska, K. Holthoff, From form to function: calcium compartmentalization in dendritic spines, Nat. Neurosci. 3 (2000) 653–659.