Spring 2011

Alzheimer's Disease and Mild Cognitive Impairment: A Review of Etiology, Clinical Diagnosis, and the Involvement of Dendritic Spines

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting a range of cognitive faculties, for which there is currently no treatment, save for ameliorative strategies. This disease primarily affects the elderly, and is the leading cause of dementia among this group. Out of an estimated 5.4 million Americans with AD this year, 5.2 million are over the age of 65. With the amount of people aged 65 and older increasing as the Baby Boomer generation ages, AD will become an increasingly dire burden. As we face this growing issue, research into both its causes and more sensitive and accurate diagnostic tools abounds.[1] This research progresses in tandem with efforts to more accurately describe, identify, and understand a prodromal, transitional state between normal cognition and Alzheimer's dementia called Mild Cognitive Impairment (MCI). MCI comprises a number of sub-types, one of which (amnestic MCI) having a marked association with later progression to frank AD.[2] This introduction will offer a summary of these conditions and the research into their etiology, clinical criteria, and improved methods of earlier detection. Emphasis will later be placed on the biology of dendritic spines, including the upstream regulators of their development, and their relation to AD and MCI.

Alzheimer's disease

Causes: I. Amyloid Cascade Hypothesis, II: Alternative hypotheses

In 1906, Alois Alzheimer presented the first description of the dementia now known as Alzheimer's disease. After following the clinical development of the patient, Auguste D, Alzheimer identified upon microscopic analysis of her stained brain tissue anomalous deposits which he termed "miliary foci" and neurofibrils. These two pathological findings, now known to be senile plaques composed of amyloid-β (Aβ) and neurofibrillary tangles (NFTs) of the tau

protein respectively, were presented by Alzheimer in relation to Auguste's clinical displays of cognitive decline, and were quickly accepted as both characteristic and somehow causative of the disease's neurodegeneration and its resultant impact on cognitive faculties. Over the past century, further study has produced a general hypothesis for the pathogenesis of Alzheimer's disease termed the amyloid beta cascade, which implicates the accumulation of the Aβ peptide as the primary initiator of a sequence of cellular and sub-cellular events which eventually manifest in dementia. While this (or at least parts of it) remains the most widely accepted etiological mechanism, evidence has accumulated which suggests that the true process might be more heterogeneous, comprising a number possible avenues which converge at the precipitation of dementia, for which the pathological findings of senile plaques and NFTs are not as much primary instigators as they are coincident with and perhaps subsequent to different processes.[3] In the following sections, the amyloid cascade hypothesis will first be described and its evidential support summarized, after which other hypotheses will be likewise delineated.

I: Amyloid Cascade Hypothesis

The generation of senile plaques and neurofibrillary tangles has long been a focus of research, and much has been learned about how these structures arise. Senile plaques are aggregates of primarily the protein amyloid-β, itself produced by the cleavage of a protein called amyloid precursor protein (APP) by the protease γ-secretase.[3,4] The sequencing of senile plaques in 1984, which revealed Aβ as their primary constituent, coupled with the identification of mutations in the *APP* gene encoding APP as causative of familial AD in 1991 laid the groundwork for what is now called the amyloid cascade hypothesis by appearing to clearly indict Aβ deposition as the basic initiator of the disease.[4] The two biggest players in this hypothesis are senile plaques and NFT's, so it is natural to begin with an introduction to these components.

Observational evidence for the accumulation of Aβ instigating or supporting the onset of AD has been abundant, comprising Alzheimer's own findings a century ago, as well as the discovery of mutations in genes directly related to Aβ production that cause early onset, familial AD. These genes include APP and presenilin-1 and presenilin-2. Mutation in APP invariably produced early onset AD, thought the exact mechanism by which this occurs is unknown. Presenilin-1 and -2 both constitute a portion of γ-secretase, a proteolytic enzyme that cleaves Aβ from APP prior to its export. A number of mutations in presenilin-1 and -2 have been demonstrated as causative of early onset AD, and in fact cause the majority of early onset familial AD. While the disease process in late onset, sporadic AD (absent the aforementioned mutations) is more complicated than the early onset disease, these mutations constitute strong evidence for Aβ being an integral player, and have informed much of the study into Aβ toxicity and its role in sporadic AD.[15]

As Aβ peptide fragments are liberated from APP by γ-secretase, they begin to agglomerate extracellularly into dimers, trimers, and greater-n oligomers. The resultant senile plaques have been shown to primarily associate with the postsynaptic components of synapses, the majority of which are dendritic spines. Marked decreases (in general) in synaptic and spine integrity have been observed. While the exact mechanism of this selective toxicity towards postsynaptic structure and function remains unknown, a number of experimental models have shown Aβ plaques, and to a greater extent, smaller oligomeric soluble fragments, to mediate their effects via certain postsynaptic receptors, including prion protein, metabotropic glutamate receptors (mGluRs), and NMDA receptors.[5] NMDA receptors are of particular import given their roles in excitatory glutamate neurotransmission and participation in pathways affecting mitochondrial function. Studies have shown that Aβ oligomer association with NMDA receptors

results in the activation of signaling pathways leading to an increase in the production of reactive oxygen species (ROS), which are ultimately responsible for impaired neuronal function and cell death. Furthermore, dysregulation of these receptors and their downstream effects mediating synaptic plasticity is observed as a result of exposure to Aβ oligomers.[6,7] Finally, studies have revealed a pathway in which the density of post-synaptic NMDA receptors is reduced as a result of a biochemical cascade ending in the endocytosis of NMDA receptors; this cascade initiated by the binding of Aβ oligomers to α7-nicotinic receptors.[8]

In addition to the presence of senile plaques, neurofibrillary tangles (NFTs) are likewise considered a hallmark characteristic of AD. NFTs are abnormal polymers of the microtubule associate protein tau (MAPT). Normally involved in stabilizing microtubules by associating with tubulin, in AD the tau proteins are found to be hyperphosphorylated, a condition in which they dissociate from tubulin and conglomerate ultimately into NFTs.[9] In the normal brain, tau is localized primarily to the axon, where it contributes to axonal transport through its association with and maintenance of microtubule structures, though it is also present in dendrites. As tau becomes hyperphosphorylated and its associations transition from mictrotubule structures to NFTs, they apparently migrate to the somatodendritic domain. Studies have also established normal tau as a potentially important player in the dendritic spine, contributing to the maintenance of scaffolding proteins (including microtubules) that help regulate spine formation and plasticity. Additionally, pathogenic tau (hyperphosphorylated) has been shown to instigate a pathway that ultimately modifies NMDA receptors to be more susceptible to Aβ-meditated synaptotoxicity. Therefore, tau has been implicated in the disease process both by its loss of beneficial functions and its gained function in facilitating Aβ synaptotoxicity.[5]

The amyloid cascade hypothesis argues that a series of events beginning with Aβ accumulation, and in which the hyperphosphorylation and accumulation of MAPT into NFTs are the most prominent of a number of related events, ultimately ends in neurodegeneration and dysfunction.[3] As described above, Aβ oligomers cause a number of these downstream synaptic issues, including excitotoxicity, alterations of membrane receptor stoichiometry (in particular of NMDARs), and dysregulation of postsynaptic signaling leading to oxidative stresses.[5,8] Also central to this sequence is the role of neuroinflammation, a conclusion that has been somewhat contentious, as described below.

While some epidemiological studies have credited the long term use of non-steroidal anti-inflammatory drugs (NSAIDs) with reducing the risk for developing AD, others have found contradictory results. [10,11] Proliferation of microglia (primary, glial immune cells of the central nervous system) and astrocytes (glial supportive cells in the central nervous system) in association with senile plaques has also been observed, with microglial cells testing positive for numerous proinflammatory factors. These factors are known to include species that can initiate neuronal death, including prostaglandins and nitric oxide. Furthermore, microglia and astrocytes are capable of sensing Aβ through a number of toll-like receptors (TLR2, TLR4, and TLR9) expressed on their surfaces. Consensus on the ultimate results of microglial activation via this Aβ detection has been elusive, as different studies have suggested that microglial activation may facilitate their recognition and clearance of senile plaques and thus proffer neuroprotection, while others support the notion that their activation induces immuno-inflammatory responses that further damage neurons.[12] Recent studies have further supported the notion that microglia play a neuroprotective role in at least some capacity. At least two studies involving the administration of factors that initiate the production and recruitment of microglia (primarily from

the bone marrow as opposed to those endogenous to the brain) have reported reduced amyloidosis (Aβ deposition) and cognitive decline in mouse models of AD.[13,14] While there remains no clear consensus of the role of inflammatory and immune responses in AD, it is clear that these processes are unlikely to represent a black and white mechanism of exclusive protection or harm, and the inducement of inflammation by Aβ nonetheless remains in general a canonical event in the amyloid cascade hypothesis.

To summarize, the most comprehensively described hypothesis to explain the progression of Alzheimer's disease is that of the amyloid cascade. Chronologically, Aβ deposition as a result of either greater production due to genetic mutations (APP, presenilin-1 and -2) or due to some other undefined failure to clear Aβ fragments adequately, initiates early synaptic dysfunction, followed by further plaque formation; inflammation via astrocytic and microglial activation; signal cascade dysregulation leading to oxidative stress, changes in post-synaptic receptors, and the hyperphosphorylation of MAPT and subsequent production of NFTs; and ultimately neuronal death as a result of the continuation and exacerbation of the above processes. Despite its widespread support, there remain some difficulties with the amyloid cascade hypothesis. Perhaps foremost among these is that correlation between senile plaques and AD is not in itself very descriptive; i.e., the amount of senile plaque pathology is a poor measure of the severity and progression of AD symptoms, and the finding of Aβ pathology in non-demented individuals further stresses this disconnect. Adding to the uncertainty are conflicting results from studies investigating various predictions made by the hypothesis regarding the effects of the insoluble senile plaques, though the hypothesis has adapted to incorporate the effects of the smaller soluble oligomers of Aβ described above.[16] While the finer points of this hypothesis (such as the role of inflammation, also described above) still require further elucidation, the majority of attempts to

synthesize current findings in AD produce sequences resembling the amyloid cascade; the most variability from model to model concerns the earliest phases of the disease and the participation of neuroinflammation.[3]

II: Alternative Syntheses

The association of amyloid deposition with the development of Alzheimer-type dementia (as opposed to other dementias) has pervaded scientists' efforts to describe the pathogenesis of AD, eventually yielding the amyloid cascade hypothesis. In response to the weaknesses of the amyloid cascade hypothesis touched on in the previous section, recent work has sought to reevaluate the causes and mechanisms that lead to AD, using other risk factors as a starting-off point. Inspired by the identification of a number of cardiovascular conditions as risk factors common to AD, metabolic syndrome, and cerebrovascular dementia, a number of researchers have endorsed a vascular hypothesis for AD.[17]

Beginning in the early 1990's researchers, especially J. C. de la Torre, began to synthesize an array of related evidences into a hypothesis to explain AD that incriminates a loss of adequate cerebral perfusion as the primary initiator of the AD pathological cascade. Electron microscopy had revealed that, compared to age-matched controls, many small blood vessels in AD brains were in significantly poorer condition. Studies using imaging scans that can determine the rates of glucose metabolism (PET) and oxygen demand (SPECT) had found that these parameters are reduced significantly in regions of AD brains that correspond with classic senile plaque and NFT pathology; these conditions are also localized to regions which receive less-than-adequate blood supply. A deficit in glucose transporters in neurons, glia and surrounding microvessels, appears in AD, relative to controls. Finally, the concentrations of a number of

important biochemicals including proteins, neurotransmitters, and enzymes are lower in AD brains.[18]

In light of this aggregate data, J. C. de la Torre offered the earliest comprehensive vascular hypothesis of AD, in which microvascular integrity is compromised over time, leading to disturbances in blood flow rates and nutrient delivery, and initiation of reactive gliosis due to the release of astroglial mitogens by cells suffering nutrient deprivation. This astroglial proliferation is thought to have a number of downstream effects, including senile plaque and NFT formation, decreased inability of the CNS to clear waste products, and other related consequences. The pyramidal CA1 neurons appear to be particularly sensitive to these effects early on, which coincides with the earliest cognitive symptoms of AD (described in a later section).[18]

Epidemiological studies have shown support for an association between AD and a wide range of vascular conditions. Considered chief among these are cerebrovascular disease (stroke), cardiac disease, and atherosclerosis. Strokes, in particular cortical microinfarcts and silent strokes, can be closely associated with AD, with silent stroke patients in one study showing almost twice the risk of developing AD as the baseline. Numerous cardiac conditions show strong association with dementia, including AD and a related dementia known as vascular dementia (the differentiation of which is less solid in the vascular hypothesis compared to the amyloid cascade). These include myocardial infarction, hypertension, and arrhythmias, as well as some cardiac surgeries, especially coronary artery bypass graft. Atherosclerosis and its attendant sequalae, including hypoperfusion of the brain and damage to endothelial and perivascular cells of vessels bearing high atherosclerotic plaque loads, constitute significant risk factors for AD and vascular dementia. Furthermore, studies have shown that cognitive impairment associated with

chronic cerebral hypoperfusion can be ameliorated following endarterectomy, a procedure in which atherosclerotic plaque is surgically removed from the carotid artery.[17] Collectively, these epidemiological results are important to understanding AD, and they must be explained by any prospective hypothesis of the disease.

Alzheimer's Disease - Clinical Criteria and Diagnostic Methods

As our understanding of the biological processes involved in AD constantly evolves in response to new research developments, so are the criteria for diagnosing AD clinically, and, as will be discussed, potentially pre-clinically. Historically, the most authoritative diagnosis of AD has been dependant on the pathological findings of senile plaques and NFTs upon autopsy.[15] As this is, naturally, post-mortem, it is of no functional use to the patient, and so rigorous standards for a clinical diagnosis are enumerated by two main sources, the Diagnostic Statistical Manual, Fourth Edition (DSMIV) and the National Institute of Neurologic, Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). These remain the clinical criteria by which AD is identified. Recently, parallel methods of detecting and monitoring AD have been investigated, and include neuroimaging, functional neuroimaging, and peripheral biomarkers.[19] Here, the clinical presentation, criteria, and evolving detection methods for AD will be summarized.

The first cognitive faculty to be impacted in AD is most often memory – specifically, episodic memory and autobiographical memory. Language can also begin to show deficits, wherein a patient may be able to maintain the ability to speak clearly but without real substance and with subtle aphasia. Topographical memory impairments also appear, with patients getting lost more often, and other daily activities requiring visuospacial faculties, such as dressing and hygiene, can suffer.[20] Additionally, changes in personality and judgment can occur, as well as

delusions, hallucinations, and aggression.[15,20] It is important to note that the earliest manifestations can be disparate among the population depending on the specific areas that become involved.[15]

Both the DSM IV criteria and the NINCDS-ADRDA criteria require that a patient present with memory impairment accompanied by at least one other deficit from another cognitive modality. Each specifically recognizes aphasia (loss of word comprehension, searching for words), apraxia (difficulty with visuospatial motor skills like dressing or bathing), agnosia (problems recognizing known objects), and dysexecutive functioning (inability to plan and execute normal activities) as potential cognitive consequences. These criteria further require that these deficits represent a significant impact on a patient's daily social and/or occupational functioning, and present without any other neurological issues identified through a normal neurological exam.[15,19]

Early and accurate diagnosis is naturally of paramount importance in providing patients with optimum treatment and management. The above clinical criteria have received some criticism (as expressed even in their original proposals) for having less-than-ideal specificity in AD diagnosis despite having fairly good accuracy. Estimates of the accuracy of these criteria, as measured by validation by neuropathological assessment post-mortem, fall within the range of 65-96%; specificity estimates, however, are much less encouraging, with a range of 23-88%. As the phenotype of AD shares similarities with a number of non-AD dementias, it is not surprising that methods relying on clinical presentation might have compromised specificity. Furthermore, many of these non-AD dementias now benefit from very sensitive and specific criteria that are independent of dementia presentation; for example, diagnoses of primary progressive aphasia

can be made before dementia develops. The adjustment of the clinical criteria for AD must be likewise improved upon to increase its sensitivity pre-dementia and improve its specificity.[21]

Various neuroimaging techniques have shown promise in diagnosing AD. The assessment of volumetric changes in certain brain regions such as the hippocampus and entorhinal cortex by MRI has been evaluated. Results have been positive but still inconclusive, as these changes can be non-specific to AD.[19] Functional neuroimaging techniques, which measure the activity of the brain, have also been studied. FDG-PET and 99mTc-HMPAO-SPECT, which measure glucose metabolism and brain perfusion respectively, have both demonstrated efficacy in diagnosing AD and differentiating among dementias, though PET is less discriminatory regarding vascular dementia.[21] Furthermore, the use of PET to detect the binding of a ligand, C11-Labeled-Pittsburgh Compound B (PiB), to senile plaques, has been intriguing, though at present it suffers from less than ideal specificity (as normal controls may exhibit plaque pathology) and accuracy.[15] These techniques represent one approach to the characterization of neurological changes in the brain concurrent with and preceding onset of frank AD, and are therefore valuable avenues for the advancement of clinical identification of AD.

Finally, the ability to quantify the concentrations of Aβ peptide, total tau, and phosphorylated tau in the cerebrospinal fluid (CSF) has developed into an important tool for predicting AD. Aβ peptide is lower in the cerebrospinal fluid of AD patients than in controls, though alone is not effective as a diagnostic measure as it correlates poorly with the severity of cognitive deficit. High levels of total tau and phosphorylated tau (at wither threonine residue 181 or 231), however, have been successfully correlative with AD diagnosis.[19] The evaluation of all three markers has shown promising results, with specificities and sensitivities of at least 85% and

90% in predicting AD onset within 4 to 6 years.[21]While the assessment of these CSF biomarkers have yet to be accepted as routine tests for patients suspected of developing AD by the American Academy of Neurology, their value thus far warrants further study.[19]

As our knowledge of the etiology of AD progresses, so must our clinical characterizations of the disease. The application of multiple direct and peripheral methods for the diagnosis of AD must continue to be a focus of research, and the characterization of the earliest neurological changes associated with the progression to AD has benefitted from similar efforts. In assessing the earliest stages of AD, it has been an imperative goal to describe and understand the putative transitional condition mild cognitive impairment (MCI).

Mild Cognitive Impairment

While a single definition has remained elusive, MCI generally describes subjective or objective cognitive and/or memory deficits that are greater than expected for normal aging but fail to impede normal daily activity. Presentation of MCI constitutes a risk factor for developing frank AD, with this risk depending on which of a number of subtypes is exhibited. As this stage is by definition pre-dementia of any type, including AD, interventions aimed here would presumably hold greater therapeutic value than current treatment strategies. Here, the clinical and diagnostic criteria of MCI will be described.[21]

The subset of cognitive complaints of patients diagnosed with MCI forms the dichotomy of the MCI subtypes. Amnestic MCI is diagnosed following complaint of memory impairment; deficits in other cognitive modalities compose non-amnestic MCI. If the deficit is identified in only one area of cognition, it is termed single-domain, and, naturally, if it involves two or more areas, it is termed multiple-domain; an individual can have any combination of amnestic, non-amnestic, single-domain, or multi-domain MCI. For a diagnosis of amnestic MCI to be made, the

memory deficit must be significant with respect to age and education matched controls. In assessing mental state, it has been recommended that more specific memory tests be employed, as performance on typical examinations of mental state for identification of AD (mini-mental state examination (MMSE), modified mini mental state examination (3MS), or Kokman Short Test of Mental Status) will be close to normal.[19] Amnestic MCI has been shown to have a higher risk for progressing to AD than non-amnestic MCI, though the definitional criteria need further refinement before the diagnosis implies that prognosis with adequate specificity and sensitivity. This difficulty also applies to clinical trials of treatments aimed at preventing the progression from MCI to frank AD, because the cohorts included may not all represent prodromal AD.[21]

Given the risks for developing AD posed by MCI, a characterization of the neuropathological events occurring in MCI, and thus before the presentation of any dementia, has been a priority. Many studies have demonstrated that the brains of MCI subjects examined post-mortem display varying degrees of senile plaque and vascular pathology, all occupying the range between normal controls and AD subjects, and smaller studies have shown that both MCI and early AD brains contain NFT pathology.[21] These results support the notion that MCI represents a transitional phase between normal aging and some terminal condition, including AD. This is in spite of the fact that many MCI cohorts have included proportions of subjects for whom there was no progression, and in some even a reversal of cognitive decline [22]; these discrepancies are potentially a product of an incomplete understanding of the clinicopathological substrates of MCI, including amnestic MCI.

Assessing the underlying mechanisms of MCI and its progression to AD is extremely important, as with this understanding will come a greater ability to develop and target interventions aimed at the pre-dementia stage. One aspect of neurological functioning which has

long been studied in AD and is now being investigated in MCI – the integrity of dendritic spines – is a crucial part of any model of the disease.

Dendritic Spines in AD and MCI

Along dendritic lengths, the majority of excitatory synapses occur at small compartmentalized protrusions of the dendritic membrane called spines. Spines represent a substrate for learning and memory, as their number and configuration is dynamic and responsive to a number of stimuli. Spines are characterized by a number of shapes, with varying sizes of spine necks and heads; spine heads constitute the post-synaptic components of excitatory synapses and thus contain receptors for neurotransmission, of which AMPA and NMDA are types of interest. Spines have long been known to be affected in AD, and so their assessment in and before AD has been extensively described.[23] Here, the effects of AD and MCI on spines will be summarized, followed by a discussion of the sensitivity of these structures and the protein mechanisms controlling their development to Aβ oligomers.

The loss of dendritic spines, representing a loss of synapses, has been shown to better correlate with cognitive decline in AD than do evaluations of senile plaque burden. Through electron microscopy studies, immunohistochemical assessments of synaptic protein densities, and visualization of neurons through Golgi staining this synaptic loss has been well characterized. While the exact mechanism behind these changes is still unclear, studies investigating the effects of Aβ peptides on spines via the NMDA receptor, as well as studies examining the relative expression of synaptic proteins have provided some groundwork. Aβ oligomers have been shown to interact specifically with NMDA receptors (as described in part above), and to further cause a reduction in spine density and NMDA number, with the former effect requiring the latter.[23] In one study using human tissue, a reduction in synapse density in

the hippocampal CA1 neurons in mild AD, as well as in MCI, was reported. Both showed synapse loss relative to non-cognitively impaired controls, with the greater of the two reductions seen in mild AD.[24]

Measuring synaptic protein expression in AD and MCI, and in different regions of the brain, has illustrated one important facet of spine changes in AD: the changes that occur do not do so homogeneously. One investigation of the levels of synaptophysin (SYP), synaptogtagmin (SYT), and drebrin (DRB) in five regions of the human neocortex (anterior cingulate, superior frontal, superior temporal, inferior parietal, and visual), in the tissue of subjects who either had sever AD, mild AD, MCI, or no cognitive impairment, found that DRB was differentially regulated in MCI in the superior frontal cortex. DRB is a post-synaptic protein associated with the generation of spines via modulation of the actin cytoskeleton, as well as the recruitment of neurotransmitter receptors to the post-synaptic membrane. DRB was found to be decreased uniformly in AD, and in all but the superior frontal cortex, the same was true of MCI. In the superior frontal cortex of MCI subjects, DRB levels were elevated relative to both AD and normal controls. The elevation of DRB in the superior frontal cortex (a region associated with executive functioning) in MCI may explain the relative preservation of executive functioning in early AD, and the uniform loss elsewhere may likewise explain the loss of spines and resultant cognitive impairment related to those regions.[25]

Beyond DRB, the actin cytoskeleton and relevant regulators of its function in the formation and support of spines has been shown to be responsive to Aβ oligomers in both hippocampal cells *in vitro* and in mouse models of AD. The actin cytoskeleton is in part regulated by cofilin, a protein which is regulated via phosphorylation by an intermediate kinase called LIM kinase. LIM kinase is in turn activated by phosphorylation by p21-activated kinase 1,

or PAK1. Cofilin, when unphosphorylated, is active, and disrupts the assembly of actin monomers into filaments, which can lead to spine destabilization. PAK's phosphorylation of LIM kinase enables the latter to phosphorylate cofilin, inactivating it and thus supporting spine formation. Aβ oligomer has been shown to effect a downregulation of PAK1, thus facilitating the dysregulation of cofilin. Furthermore, drebrin was found to be decreased, which reinforces the role of Aβ oligomers in effecting dysregulation of upstream actin regulators and the resulting spine loss.[26]

As evidenced by the above discussions, dendritic spine loss, in both correlating highly with AD, and in being demonstrated to be the result (at least in part) of AD and MCI specific and heterogeneous changes in synaptic protein stoichiometry and Aβ mediated dysregulation of the actin cytoskeleton responsible for spine development, should remain a focus of scientific attention. As synapses are the substrate for cognitive functioning and memory, understanding how spines change and why they do so differently in different regions of the brain will illuminate potential targets for future therapeutic strategies.

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