

## Mini Review

# Dendritic Spine Modifications in Synaptic Plasticity

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## Abstract

Synaptic plasticity is regarded as the cellular mechanism underlying the refinement of neural connections during development and learning/memory functions in adults. Alterations in dendritic spine morphology (elongation or shrinkage) and/or spine density occur with synaptic plasticity. This structural modification has been proposed to enable persistent, long-term change in synapses. Here we review spine modifications associated with synaptic plasticity and discuss their contributions to synaptic plasticity and brain diseases.

**Keywords:** Synaptic plasticity; Spine morphology; Learning and memory; Brain diseases

## Abbreviations

LTP: Long-Term Potentiation; LTD: Long-Term Depression; PSD: Post Synaptic Density; AMPAR:  $\alpha$ -Amino-3-hydroxy-5-Methyl-4-isoxazole Propionic Acid Receptor; NMDAR: N-Methyl-D-Aspartate Receptor; PKA: Protein Kinase A; CaMKII: Ca<sup>2+</sup>/calmodulin-dependent protein Kinase II; PP2A: Protein Phosphatase 2; Rac1: Ras-related C3 botulinum toxin substrate 1

## Introduction

Dendritic spines are small postsynaptic structures protruding from dendrites and the primary site of excitatory input. About 90% of excitatory synapses occur on spines on the excitatory neurons in the adult cortex [1]. Spines are usually divided into three types based on the size, spine head shape, and spine neck length. Mushroom spines have large heads and constricted narrow necks, thin spines have small heads and slender necks, while stubby spines have no distinct heads and necks [2,3]. This categorization is to provide an easy classification while the actual distribution of spine shapes is of a continuum.

The recent development of two-photon imaging allows spine morphology and dynamics to be studied in great detail using time-lapse and repetitive imaging, and has enabled the study of spine alterations in response to physiological or pathological events [4,5]. For example, dendritic spines are dynamic in genesis and elimination, especially during brain development. In adolescence, spines show much higher elimination than formation which results in net spine loss or pruning. However in the adult, the rate of spine genesis and elimination is much reduced and roughly equivalent, which maintains the stability of spine density [6,7].

Spines are considered a unique calcium compartment [8]. Spine plasticity is demonstrated by their capacity to undergo both rapid (seconds) and persistent (months to years) alterations in response to either physiological or pathological events. Large spines may be the storage site of stable long-term memory [1], while filopodia are considered as the immature form of spine which can be transformed into mature spines or eliminated. Spine plasticity is exhibited in two forms: changes in spine morphology/size and changes in spine density. Both changes reflect altered synaptic connections and strength. In neurodegenerative and psychiatric diseases, spine density

and morphology are altered, and these changes may partially account for alterations in brain functions associated with these diseases. Thus a better understanding of spine pathology may provide better therapeutic intervention.

## Spine plasticity

Changes in spine density reflect an altered connection density between presynaptic and postsynaptic neurons, and this type of plasticity is most commonly observed during development (increase and decrease/pruning) and aging/degeneration (decrease). Changes in spine morphology, especially of the spine head have been documented using various methods, and is believed to be associated with changes in the strength of synapses.

Due to the heterogeneity of spine morphology, the most convincing way of demonstrating altered spine morphology is provided by comparing the same set of spines before and after synaptic plasticity-inducing stimuli in brain slices or learning *in vivo*. Many studies have examined how spines are altered with the induction of Long-Term Potentiation (LTP) and Long-Term Depression (LTD). These two forms of synaptic plasticity are generally regarded as the cellular basis of synaptic modifications [9].

## Spine modifications associated with LTP

In general, spines can undergo bi-directional changes, just as synaptic alterations. Enlargement of spine heads was seen with LTP and shrinkage of spines with LTD [10-12]. The same spines can undergo enlargement and shrinkage with consecutive induction of LTP and LTD [13], indicating that morphological modifications can occur in a bi-directional manner and that these changes are driven by synaptic modifications. The uncaging of caged glutamate onto a single spine [13,14] and electrical stimulation of a population of synapses/spines [15,16] supported the above conclusion.

There is generally a strong correlation between the strength of a given synapse and the size of spine. For example, Takumi *et al.* found that AMPAR density was linearly related to the diameter of Post-Synaptic Density (PSD) [17,18]. Matsuzaki *et al.* reported a large range of AMPAR numbers in spines; AMPARs were enriched in mushroom spines but were sparsely distributed on thin spines and filopodia, revealing a strong correlation between the number of AMPAR and the volume of spine head [18].

Since both an increase of synaptic strength which is mediated by increased phosphorylation and/or insertion of AMPARs into the potentiated synapses and enlargement of spine occur with LTP, a question arises as to whether functional changes are casually related to changes in morphology/structure. Are these two processes driven by the same upstream processes? Does the occurrence or persistence of one process require the other? It is well established that both processes require a Ca<sup>2+</sup> influx through the synaptic NMDARs during LTP induction, and elevated intracellular Ca<sup>2+</sup> concentration drives AMPAR phosphorylation and/or insertion [9] and polymerization of actin filaments inside spines [12]. The initial increase in synaptic response and spine volume occurs very rapidly (< 1 min) [13,16]. Dendritic spine heads accumulate F-actin during this rapid expansion phase, and can persist for weeks together with an increase in synaptic function [19]. Potentiation of single synapse/spine with glutamate uncaging led to a significant expansion of the spine head and a shortening and widening of the spine neck [20,21]. F-actin concentration inside the spine head rises, together with the entrance of actin-severing, actin-depolymerizing/-polymerizing, actin-capping proteins while actin-stabilizing proteins leave the spines [20,22-26]. Cofilin, an actin-depolymerizing agent, is highly elevated in spines during this initial process [25]. Interestingly, unlike LTP this initial spine expansion did not require postsynaptic exocytosis or PKA signaling [16], suggesting the involvement of different signaling pathways than those supporting LTP. After initial rapid expansion, the next phase of events lasts up to 1 hour, with spine head volume declining from the initial increase, yet remaining larger than the pre-LTP baseline [25].

There is some evidence that AMPARs are not delivered directly into the PSDs inside spines, but are instead delivered to regions outside synapses (i.e., the perisynaptic regions) [28] or onto dendritic shaft [27,29]. These newly inserted AMPARs then move laterally into spines or PSDs. Yang *et al.* found that the stability of the perisynaptic AMPARs depends on the persistence of spine enlargement, that reversal of spine expansion led to the removal of perisynaptic AMPARs and absence of LTP. It is unclear as whether spine enlargement is required for the movement of these new AMPARs to PSD, or for retaining them at the PSD. Yang *et al.* also demonstrated that the converse is true that moving of the newly inserted AMPARs to the synapse is required for persistent spine enlargement [28]. Thus, an insurance mechanism is in place for coordinated modifications in synaptic function and spine morphology, i.e., matched changes in physiology and structure. Furthermore, if one process does not occur, the other process will be aborted even in progress. This double-proof mechanism is essential to ensure that only appropriate changes (i.e., coordinated changes) are allowed to become persistent. This mechanism may be especially important in face of the highly dynamic nature of synaptic modifications, such as those occurring during early brain development [29]. About 1 hour after LTP induction, PSD scaffolds are recruited to spines to stabilize the newly added synaptic AMPARs [25]. This process requires protein synthesis [30].

Another mechanism to alter connections between neurons is to change synapse density. In that context, it has been shown that new spines emerged with the induction of LTP, and some of the new spines contribute to the increase in synaptic connection [31,32]. These new spines first appear in an immature form resembling filopodia,

they later become mature (mushroom like spines), or are eliminated. A good indication that the new spines will be maintained is if they process synapses [32,33]. Stabilization of these newly generated spines requires the activation of NMDARs and CaMK II signaling [33]. In addition to the de novo genesis of new spines, splitting of potentiated spines also occur with LTP [12,34]. Note that LTP also induces alterations in axonal morphology and actin cytoskeleton leading to genesis of new axonal varicosities and new puncta [35,36].

### Spine modifications associated with LTD

LTD is associated with spine shrinkage, opposing spine enlargement [22,37]. In the initial stage, a Ca<sup>2+</sup> influx through the activated NMDARs is required for both LTD and spine shrinkage [15,37]. Similar to LTP/spine enlargement, some signaling events (NMDAR activation, elevation of calcineurin activity and postsynaptic depolymerization) are shared by both processes, while others are differentially required for either LTD expression (elevated PP-2A activity) or spine shrinkage (elevated cofilin activity) [15,22,37,38]. In support of this conclusion, Sdrulla and Linden demonstrated a double dissociation between LTD expression and spine changes in cerebellar Purkinje cells [39]. Interestingly, Wang *et al.* revealed that activity-independent constitutive trafficking of AMPARs to and away from PSDs was not associated with changes in spine size, but the significance of this observation remains unclear [15].

Sustained reduction in synaptic strength may eventually lead to the loss of synaptic connections, and this loss is manifested as a reduction in spine density. Spine loss appears to be a protracted process and thus is difficult to study. Nonetheless, a few studies have attempted to examine this process. By using organotypical slices and monitoring both presynaptic boutons and spines, Becker *et al.* showed that LTD induction enhanced the turnover rate of presynaptic boutons and led to reduced contacts between the pre- and post-synaptic sites. Although the disappearance rate of presynaptic boutons and postsynaptic spines were greatly elevated after LTD induction, the sequence of events did not appear to follow a particular pattern, as disappearance of either presynaptic boutons or spines was observed to occur prior to the other [40]. These observations suggest that the exact sequence of events may not matter much, as long as there is a mismatch between the two sites.

### Learning and memory *in vivo*

The ultimate proof that spine modifications have significant contributions to physiological process must come from *in vivo* studies, by comparing the same set of spines before and after the occurrence of a physiological process (such as learning or memory). By using time-lapse two-photon imaging on the same set of spines, Yang *et al.* discovered that new spines were formed after *in vivo* experience (sensory or motor), and a fraction of these new spines persisted for months [41]. More importantly, the genesis of new spines is specific to the experience or training, rather than other non-specific factors. Hayashi-Takagi *et al.* showed that motor learning (rotarod) resulted in enhanced Arc signaling and spine expansion in a subset of spines in the motor cortex [42]. By expressing a photo activatable GTPase Rac1 in spines, they showed that prolonged photo-activation led to spine shrinkage (reversed expansion) and loss of recently-acquired motor memory. This is a striking demonstration that enlarged spines are underlying the stored memory and reversing these changes “erased” memory.

## Alterations of dendritic spines in brain disorders

It has been convincingly demonstrated that spine alterations occur in various brain diseases, including neurodegenerative diseases and psychiatric disorders. Here we will review briefly evidence of their occurrence and potential contribution to pathology in Alzheimer's disease and schizophrenia.

### Alzheimer's disease

Individuals with early-onset Alzheimer's disease had significantly fewer synapses in the inferior temporal gyrus, CA1, dentate gyrus, and posterior cingulate gyrus [43-45]. Spine genesis is likely impaired in AD mice. For example, enriched environment was shown to elevate spine density in wt mice, but failed to do in AD mice [46] and immunohistochemical analysis showed loss of the presynaptic marker synaptophysin [47]. Major contributing factor in spine loss in AD is the presence of amyloid plaque. Numerous studies on both human post-mortem samples and AD transgenic mice have shown that spine loss preferentially occurs in regions near the amyloid plaques [48-50].

In addition, substantial axonal damage is present at the fibrillar plaques [51], which may cause spine loss. It has been shown that the level of oligomer form of A $\beta$  is correlated with the degree of synapse loss [52], suggesting that A $\beta$  oligomers may be a direct culprit in spine loss. Supporting this hypothesis, immunotherapy directed against oligomeric A $\beta$  abolished synapse loss in Tg2576 mice [53]. In addition, many of the identified targets of A $\beta$  are associated with synapses [54-57].

### Psychiatric disorders Schizophrenia

Spine loss in neurodegeneration and aging is easy to comprehend. Significant spine loss also occurs in other brain diseases, such as psychiatric disorders, most of which have developmental origins.

Reduced spine density in multiple areas within the frontal and temporal neocortex has been reported in schizophrenia patients [58,59]. Dendritic arborization is also decreased with reduction of dendrite length, field size and dendrite number [60,61]. During adolescence, spine genesis dominates over spine elimination. But there is a net spine reduction/elimination in schizophrenia which is likely caused by the instability of the newly formed spines [62]. In addition, the molecular machinery regulating actin skeleton function was also altered in schizophrenia patients, such as Kalirin-7, Cdc42 [63] and MAP2 [64-66].

## Conclusion

Dendritic spines play critical roles in excitatory synaptic transmission and plasticity. They are the site where physiological and morphological modifications meet and integrate. Changes in spine density and dimension contribute significantly in both physiological and pathological processes and also can serve as a marker of such processes. During the LTP, the insertion of new AMPA receptors and spine enlargement are closely related, and appear to be dependent on each other to certain extent. *In vivo* studies demonstrated that learning and memory contributes to spine genesis and morphological changes, and more importantly these changes are required to sustain memory. In neurodegenerative diseases and psychiatric disorders, the density and size of spines are altered which may contribute to pathogenesis. Based on the above evidences, signaling molecules

which regulate spine density and morphology may be potential drug targets.

## References

1. Tackenberg C, Ghori A, Brandt R. Thin, stubby or mushroom: spine pathology in Alzheimer's disease. *Curr Alzheimer Res.* 2009; 6: 261-268.
2. Peters A, Kaiserman-Abramof IR. The small pyramidal neuron of the rat cerebral cortex. The perikaryon, dendrites and spines. *Am J Anat.* 1970; 127: 321-355.
3. Harris KM, Jensen FE, Tsao B. 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.* 1992; 12: 2685-2705.
4. Mizrahi A, Crowley JC, Shtoyerman E, Katz LC. High-resolution *in vivo* imaging of hippocampal dendrites and spines. *J Neurosci.* 2004; 24: 3147-3151.
5. Grutzendler J, Kasthuri N, Gan WB. Long-term dendritic spine stability in the adult cortex. *Nature.* 2002; 420: 812-816.
6. Holtmaat AJ, Trachtenberg JT, Wilbrecht L, Shepherd GM, Zhang X, Knott GW, *et al.* Transient and persistent dendritic spines in the neocortex *in vivo*. *Neuron.* 2005; 45: 279-291.
7. Zuo Y, Lin A, Chang P, Gan WB. Development of long-term dendritic spine stability in diverse regions of cerebral cortex. *Neuron.* 2005; 46: 181-189.
8. Korkotian E, Segal M. Structure-function relations in dendritic spines: is size important? *Hippocampus.* 2000; 10: 587-595.
9. Malenka RC, Nicoll RA. Long-term potentiation—a decade of progress? *Science.* 1999; 285: 1870-1874.
10. Wang XB, Zhou Q. Spine remodeling and synaptic modification. *Mol Neurobiol.* 2010; 41: 29-41.
11. Yang Y, Zhou Q. Spine modifications associated with long-term potentiation. *Neuroscientist.* 2009; 15: 464-476.
12. Yuste R, Bonhoeffer T. Morphological changes in dendritic spines associated with long-term synaptic plasticity. *Annu Rev Neurosci.* 2001; 24: 1071-1089.
13. Kasai H, Matsuzaki M, Noguchi J, Yasumatsu N, Nakahara H. Structure–stability–function relationships of dendritic spines. *Trends Neurosci.* 2003; 26: 360-368.
14. Harvey CD, Yasuda R, Zhong H, Svoboda K. The spread of Ras activity triggered by activation of a single dendritic spine. *Science.* 2008; 321: 136-140.
15. Wang XB, Yang Y, Zhou Q. Independent expression of synaptic and morphological plasticity associated with long-term depression. *J Neurosci.* 2007; 27: 12419-12429.
16. Yang Y, Wang XB, Frerking M, Zhou Q. Spine expansion and stabilization associated with long-term potentiation. *J Neurosci.* 2008; 28: 5740-5751.
17. Takumi Y, Ramirez-Leon V, Laake P, Rinvik E, Ottersen OP. Different Modes of Expression of AMPA and NMDA Receptors in Hippocampal Synapses. *Nat Neurosci.* 1999; 2: 618-624.
18. Matsuzaki M, Ellis-Davies GC, Nemoto T, Miyashita Y, Iino M, Kasai H. Dendritic spine geometry is critical for AMPA receptor expression in hippocampal CA1 pyramidal neurons. *Nat Neurosci.* 2001; 4: 1086-1092.
19. Fukazawa Y, Saitoh Y, Ozawa F, Ohta Y, Mizuno K, Inokuchi K. Hippocampal LTP Is Accompanied by Enhanced F-Actin Content Within the Dendritic Spine That is Essential for Late LTP Maintenance *in vivo*. *Neuron.* 2003; 38: 447-460.
20. Matsuzaki M, Honkura N, Ellis-Davies GC, Kasai H. Structural basis of long-term potentiation in single dendritic spines. *Nature.* 2004; 429: 761-766.
21. Tonnesen J, Katona G, Rozsa B, Nagerl UV. Spine neck plasticity regulates compartmentalization of synapses. *Nat Neurosci.* 2014; 17: 678-685.
22. Okamoto K, Nagai T, Miyawaki A, Hayashi Y. Rapid and persistent modulation



- of actin dynamics regulates postsynaptic reorganization underlying bidirectional plasticity. *Nat Neurosci.* 2004; 7: 1104-1112.
23. Honkura N, Matsuzaki M, Noguchi J, Ellis-Davies GC, Kasai H. The subspine organization of actin fibers regulates the structure and plasticity of dendritic spines. *Neuron.* 2008; 57: 719-729.
  24. Mizui T, Sekino Y, Yamazaki H, Ishizuka Y, Takahashi H, Kojima N, *et al.* Myosin II ATPase activity mediates the long-term potentiation-induced exodus of stable F-actin bound by drebrin A from dendritic spines. *PLoS One.* 2014.
  25. Bosch M, Castro J, Saneyoshi T, Matsuno H, Sur M, Hayashi Y. Structural and molecular remodeling of dendritic spine substructures during long-term potentiation. *Neuron.* 2014; 82: 444-459.
  26. Meyer D, Bonhoeffer T, Scheuss V. Balance and stability of synaptic structures during synaptic plasticity. *Neuron.* 2014; 82: 430-443.
  27. Makino H, Malinow R. AMPA receptor incorporation into synapses during LTP: the role of lateral movement and exocytosis. *Neuron.* 2009; 64: 381-390.
  28. Yang Y, Wang XB, Frerking M, Zhou Q. Delivery of AMPA receptors to perisynaptic sites precedes the full expression of long-term potentiation. *Proc Natl Acad Sci U S A.* 2008; 105: 11388-11393.
  29. Zhou Q, Tao HW, Poo MM. Reversal and stabilization of synaptic modifications in a developing visual system. *Science.* 2003; 300: 1953-1957.
  30. Tanaka J, Horiike Y, Matsuzaki M, Miyazaki T, Ellis-Davies GC, Kasai H. Protein synthesis and neurotrophin-dependent structural plasticity of single dendritic spines. *Science.* 2008; 319: 1683-1687.
  31. Engert F, Bonhoeffer T. Dendritic spine changes associated with hippocampal long-term synaptic plasticity. *Nature.* 1999; 399: 66-70.
  32. Knott GW, Holtmaat A, Wilbrecht L, Welker E, Svoboda K. Spine growth precedes synapse formation in the adult neocortex *in vivo*. *Nat Neurosci.* 2006; 9: 1117-1124.
  33. Hill TC, Zito K. LTP-induced long-term stabilization of individual nascent dendritic spines. *J Neurosci.* 2013; 33: 678-686.
  34. Bourne JN, Harris KM. Balancing structure and function at hippocampal dendritic spines. *Annu Rev Neurosci.* 2008; 31: 47-67.
  35. De Paola V, Arber S, Caroni P. AMPA receptors regulate dynamic equilibrium of presynaptic terminals in mature hippocampal networks. *Nat Neurosci.* 2003; 6: 491-500.
  36. Colicos MA, Collins BE, Sailor MJ, Goda Y. Remodeling of synaptic actin induced by photoconductive stimulation. *Cell.* 2001; 107: 605-616.
  37. Zhou Q, Homma KJ, Poo MM. Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. *Neuron.* 2004; 44: 749-757.
  38. Halpain S, Hipolito A, Saffer L. Regulation of F-actin stability in dendritic spines by glutamate receptors and calcineurin. *J Neurosci.* 1998; 18: 9835-9844.
  39. Sdrulla AD, Linden DJ. Double dissociation between long-term depression and dendritic spine morphology in cerebellar Purkinje cells. *Nat Neurosci.* 2007; 10: 546-548.
  40. Becker N, Wierenga CJ, Fonseca R, Bonhoeffer T, Nagerl UV. LTD induction causes morphological changes of presynaptic boutons and reduces their contacts with spines. *Neuron.* 2008; 60: 590-597.
  41. Yang G, Pan F, Gan WB. Stably maintained dendritic spines are associated with lifelong memories. *Nature.* 2009; 462: 920-924.
  42. Hayashi-Takagi A, Yagishita S, Nakamura M, Shirai F, Wu YI, Loshbaugh AL, *et al.* Labelling and optical erasure of synaptic memory traces in the motor cortex. *Nature.* 2015; 525: 333-338.
  43. Scheff SW, Price DA, Schmitt FA, DeKosky ST, Mufson EJ. Synaptic alterations in CA1 in mild Alzheimer disease and mild cognitive impairment. *Neurology.* 2007; 68: 1501-1508.
  44. Scheff SW, Price DA, Schmitt FA, Mufson EJ. Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment. *Neurobiol Aging.* 2006; 27: 1372-1384.
  45. Scheff SW, Price DA, Schmitt FA, Scheff MA, Mufson EJ. Synaptic loss in the inferior temporal gyrus in mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis.* 2011; 24: 547-557.
  46. Zou C, Shi Y, Ohli J, Schuller U, Dorostkar MM, Herms J. Neuroinflammation impairs adaptive structural plasticity of dendritic spines in a preclinical model of Alzheimer's disease. *Acta Neuropathol.* 2016; 131: 235-246.
  47. Masliah E, Terry RD, DeTeresa RM, Hansen LA. Immunohistochemical quantification of the synapse-related protein synaptophysin in Alzheimer disease. *Neurosci Lett.* 1989; 103: 234-239.
  48. Hanson JE, Meilandt WJ, Gogineni A, Reynen P, Herrington J, Weimer RM, *et al.* Chronic GluN2B antagonism disrupts behavior in wild-type mice without protecting against synapse loss or memory impairment in Alzheimer's disease mouse models. *J Neurosci.* 2014; 34: 8277-8288.
  49. Spires TL, Meyer-Luehmann M, Stern EA, McLean PJ, Skoch J, Nguyen PT, *et al.* Dendritic spine abnormalities in amyloid precursor protein transgenic mice demonstrated by gene transfer and intravital multiphoton microscopy. *J Neurosci.* 2005; 25: 7278-7287.
  50. Tsai J, Grutzendler J, Duff K, Gan WB. Fibrillar amyloid deposition leads to local synaptic abnormalities and breakage of neuronal branches. *Nat Neurosci.* 2004; 7: 1181-1183.
  51. Adalbert R, Nogradi A, Babeto E, Janeckova L, Walker SA, Kerschensteiner M, *et al.* Severely dystrophic axons at amyloid plaques remain continuous and connected to viable cell bodies. *Brain.* 2009; 132: 402-416.
  52. Koffie RM, Hashimoto T, Tai HC, Kay KR, Serrano-Pozo A, Joyner D, *et al.* Apolipoprotein E4 effects in Alzheimer's disease are mediated by synaptotoxic oligomeric amyloid-beta. *Brain.* 2012; 135: 2155-2168.
  53. Dorostkar MM, Burgold S, Filser S, Barghorn S, Schmidt B, Anumala UR, *et al.* Immunotherapy alleviates amyloid-associated synaptic pathology in an Alzheimer's disease mouse model. *Brain.* 2014; 137: 3319-3326.
  54. Benilova I, De Strooper B. Neuroscience. Promiscuous Alzheimer's amyloid: yet another partner. *Science.* 2013; 341: 1354-1355.
  55. Larson ME, Lesne SE. Soluble Aβ oligomer production and toxicity. *J Neurochem.* 2012; 120: 125-139.
  56. Benilova I, Karran E, De Strooper B. The toxic Aβ oligomer and Alzheimer's disease: an emperor in need of clothes. *Nat Neurosci.* 2012; 15: 349-357.
  57. Zempel H, Mandelkow EM. Linking amyloid-beta and tau: amyloid-beta induced synaptic dysfunction via local wreckage of the neuronal cytoskeleton. *Neurodegener Dis.* 2012; 10: 64-72.
  58. Kolluri N, Sun Z, Sampson AR, Lewis DA. Lamina-specific reductions in dendritic spine density in the prefrontal cortex of subjects with schizophrenia. *Am J Psychiatry.* 2005; 162: 1200-1202.
  59. Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Arch Gen Psychiatry.* 2000; 57: 65-73.
  60. Kalus P, Muller TJ, Zuschratter W, Senitz D. The dendritic architecture of prefrontal pyramidal neurons in schizophrenic patients. *Neuroreport.* 2000; 11: 3621-3625.
  61. Broadbelt K, Byne W, Jones LB. Evidence for a decrease in basilar dendrites of pyramidal cells in schizophrenic medial prefrontal cortex. *Schizophr Res.* 2002; 58: 75-81.
  62. Chen CC, Lu J, Zuo Y. Spatiotemporal dynamics of dendritic spines in the living brain. *Front Neuroanat.* 2014; 8: 28.
  63. Hill JJ, Hashimoto T, Lewis DA. Molecular mechanisms contributing to dendritic spine alterations in the prefrontal cortex of subjects with schizophrenia. *Mol Psychiatry.* 2006; 11: 557-566.
  64. Arnold SE, Lee VM, Gur RE, Trojanowski JQ. Abnormal expression of two Microtubule-Associated Proteins (MAP2 and MAP5) in specific subfields of the hippocampal formation in schizophrenia. *Proc Natl Acad Sci U S A.* 1991; 88: 10850-10854.

65. Jones LB, Johnson N, Byne W. Alterations in MAP2 immunocytochemistry in areas 9 and 32 of schizophrenic prefrontal cortex. *Psychiatry Res.* 2002; 114: 137-148.
66. Rosoklija G, Keilp JG, Toomayan G, Mancevski B, Haroutunian V, Liu D, *et al.* Altered subicular MAP2 immunoreactivity in schizophrenia. *Prilozi.* 2005; 26: 13-34.