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Dendritic spines and their role in the pathogenesis of neurodevelopmental and neurological disorders

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Abstract: Since Cajal introduced dendritic spines in the 19th century, they have attained considerable attention, especially in neuropsychiatric and neurologic disorders. Multiple roles of dendritic spine malfunction and pathology in the progression of various diseases have been reported. Thus, it is inevitable to consider these structures as new therapeutic targets for treating neuropsychiatric and neurologic disorders such as autism spectrum disorders, schizophrenia, dementia, Down syndrome, etc. Therefore, we attempted to prepare a narrative review of the literature regarding the role of dendritic spines in the pathogenesis of aforementioned diseases and to shed new light on their pathophysiology.

Keywords: dendritic spines; autism; Alzheimer’s disease; schizophrenia

1 Introduction

Morphogenesis of the dendrites is a complex process, including the development of dendritic branches, the formation of dendritic arbors, and dendritic spines (Kulkarni and Firestein 2012). Dendritic spines are small protrusions along dendrites first described in the late 19th century by Santiago Ramon y Cajal. He visualized dendritic spines as morphological processes on the surface of the Purkinje neurons of the cerebellum and called them “Espina” or short spines (Tan 2015).

These protrusions (Figure 1) allow neurons to communicate with each other and most glutamatergic synapses are localized to dendritic spines in the mammalian brain. Three types of dendritic spine morphology have been seen in frozen snapshots, including stubby dendritic spines (attached directly to the shaft of the dendrite with no neck), mushroom spines (a large head on a thin neck), and thin dendritic spines (which have small heads attached to long thin necks). These structures are highly regulated and respond to sensory input vigorously. Signals from the environment and resultant synaptic activity lead to changes that make dendritic spine morphology so dynamic. Thus, throughout the animal’s lifespan and even adulthood, the dendritic spine’s morphology changes depending on its experiences (Holtmaat and Svoboda 2009; Penzes and VanLeeuwen 2011; Peters and Kaiserman-Abramof 1970; Taneja and Ganesh 2021; VanLeeuwen and Penzes 2012).

The shape and structure of dendritic spines play a crucial role in the function, strength, plasticity, and patterns of connections in neuronal circuits. As these factors are linked to learning and memory, any abnormalities in dendritic spine morphology, density, and plasticity can lead to deficits in neuronal connectivity across the network (Penzes and VanLeeuwen 2011; Peters and Kaiserman-Abramof 1970; Taneja and Ganesh 2021; VanLeeuwen and Penzes 2012), resulting in numerous neuropsychiatric and neurologic disorders with cognitive impairment (Blanpied and Ehlers 2004; Bourne and Harris 2008; Chen 2014; Penzes and VanLeeuwen 2011).

Experimental models demonstrate the cardinal role of dendritic spine deficits in the dysfunction of working memory, sensory-motor processing, attention, and sociability (Cahill et al. 2009; Enriquez-Barreto et al. 2012; Hains et al. 2009; Liston et al. 2006). Cognitive and memory dysfunction in Alzheimer’s disease (AD), perception, cognition, and motivation impairments in schizophrenia (SCZ), and behavioral deficits of the autism spectrum disorders (ASD) are known to be related to dendritic spine pathology and synaptic failure (Dorostkar et al. 2015; Glausier and Lewis 2013; Phillips and Pozzo-Miller 2015). Moreover, dendritic spines play a critical role in the regulation of calcium near
synapses and dendrites which is key to neurotransmission and neuronal plasticity (Rosado et al. 2022).

The present study reviews the impact of dendritic spine pathologies on developing neuropsychiatric and neurological disorders. In this line, we discuss candidate genes responsible for changes in dendritic spine morphology, elasticity, number, and function in excitatory synapses. Furthermore, we intend to elucidate the molecular processes involved and the role of anatomical changes in the etiology of these disorders.

It is vital to obtain detailed knowledge of dendritic spine pathologies and their role in the pathogenesis of neuropsychiatric and neurological disorders. As a result, more effective and directed therapeutic plans could be possible by better understanding the mechanisms underlying these disorders.

2 Schizophrenia

Schizophrenia is a neurodevelopmental disorder affecting 0.5–1% of people worldwide. Hallucinations, delusions, impaired thought processes, and impairment in emotional expression are the main clinical manifestations of this disorder, making it a significant socioeconomic and familial burden (Awad and Voruganti 2008; Bell 1994; Wu et al. 2005). Studies show genetic factors play an essential role in SCZ occurrence, as first-degree relatives have a 6–17 times and monozygotic twins a 40–50 times higher risk for developing SCZ (Gottesman 1991).

In patients with schizophrenia, multiple studies have observed a reduction in the total number of dendritic spines and the number of spines per dendrite in various cortical regions. Researchers have documented a decrease in the number of dendritic spines in the lower layer III of Brodmann’s area 41 and 42 in the primary auditory cortex, as well as in layer V of the prefrontal area 32, the temporal cortex, and the hippocampus (Figure 2) (Broadbelt et al. 2002; Dorph-Petersen et al. 2009; Garey et al. 1998; Glausier and Lewis 2011, 2013; Figure 1: Dendritic spines. Dendrites of brain neurons own protrusions involved in synapses called dendritic spines.)

Although no decrease happens in the dendritic spine numbers in the Purkinje cells of the cerebellum, dendritic spine density was reduced with an associated down-regulation of the terminal and distal branches of the dendrites (Mavroudis et al. 2017). The primary auditory cortex as one of the most significantly affected areas in SCZ, shows a decreased gray matter and pyramidal somal volume in imaging studies (Konopaske et al. 2015). As mentioned above, dendritic spine numbers and density are altered in this brain region, and multiple mechanisms are suggested to be the underlying reason.

Studies have found a correlation between the reduction of dendritic spine number and density in the auditory cortex with lower microtubule-associated protein-2 immunoreactivity (MAP2-IR) (Broadbelt et al. 2002; Dorph-Petersen et al. 2009; Garey et al. 1998; Glausier and Lewis 2011, 2013;
Konopaske et al. 2014; Li et al. 2015; MacDonald et al. 2017; Mavroudis et al. 2017; McKinney et al. 2019; Moyer et al. 2013; Shelton et al. 2015; Sweet et al. 2009). McKinney et al. reported that in patients with SCZ who have an average amount of MAP2-IR, normal dendritic spine density was found, suggesting a significant effect of this protein on dendritic spine density abnormalities (McKinney et al. 2019).

Moreover, a study (MacDonald et al. 2017) has shown that dendritic spine loss specifically involves the smaller dendritic spines, while the number of larger dendritic spines in layer III remains unchanged (Figure 2). They also reported that overexpression of the SCZ risk gene CACNB4 also contributes to high levels of its tryptic protein ALFDFLK, which is inversely correlated with smaller dendritic spine density.

On the other hand, dendritic spine loss in the auditory cortex is suggested to be associated with impairments in the glutamatergic pathways as the synaptic glutamate signaling network is involved in many SCZ risk loci (Konopaske and Coyle 2015). In addition, MacDonald et al. reported altered expression levels of glutamate signaling pathway proteins, including GRIA4, GRIA3, ATP1A3, and GNAQ, and a significant reduction in the co-expression of synaptic proteins (except for proteins involved in post-synaptic density), resulting in an inverse correlation between their co-expression levels and dendritic spine density (MacDonald et al. 2015).

Reduced dendritic spine and axonal bouton density, seen in SCZ, lead to a significantly higher neuronal density in layer III of the primary auditory cortex via the reduction of neuropil (Figure 2). While “neuronal density” refers to the number of neurons in a given area, neuropil refers to the intricate network of neuronal processes, such as dendrites, axons, and synapses. This reduction in neuropil could indicate changes in synaptic function and connectivity associated with schizophrenia (Dorph-Petersen et al. 2009; Sweet et al. 2009).

The correlation between dendritic spine reduction and presynaptic bouton density was investigated in a recent study (Garey et al. 1998) showing that there is no decrease in bouton density that corresponds to the reduction in dendritic spine density. In this case, synapses form between excitatory boutons and structures other than dendritic spines (axons, cell bodies, etc.). The study suggests this mismatch may cause functional impairments of the primary auditory cortex (Garey et al. 1998).

Prior studies using animal models of SCZ have shown reduced levels of messenger RNAs for two GTPases: Duo (murine Kalirin-7) and cell division cycle 42 (CDC42). These enzymes are involved in the phosphorylation of...
PAK1 (Figure 3), which causes alterations in the activity of the regulatory myosin light chain and coflin in the dendritic spines, promoting dendritic spine formation (Hotulainen and Hoogenraad 2010; MacDonald et al. 2015; Manser et al. 1994). The actin-depolymerizing activity of coflin is regulated via LIM domain-containing serine/threonine protein kinases (LIMK1 and LIMK2) which is also activated by CDC42. Thus, numerous proteins in the CDC42-PAK-LIMK pathways are suggested to play an essential role in actin cytoskeleton function and the stability of the dendritic spine morphology (Figure 3) (Chen et al. 2006; Hotulainen and Hoogenraad 2010; Manser et al. 1994; Newey et al. 2005; Parrini et al. 2002; Sumi et al. 2001). Rubio et al. (2012) examined this theory in post-mortem brain tissues of the anterior cingulate cortex and dorsolateral prefrontal cortex (DLPFC) of patients with schizophrenia. The results indicate a decrease in the expression of Duo, a Rho guanine nucleotide exchange factor that regulates Rac1 activity, and a reduction in PAK1 phosphorylation in both regions (Figures 2 and 3) (Joberty et al. 2001; Rubio et al. 2012).

Furthermore, many other studies have reported dendritic spine alterations in the prefrontal cortex, especially the DLPFC of patients with SCZ (Figure 2). For instance, a study (Broadbelt et al. 2006) observed a significant reduction of neurogranin levels in layers III and V of area nine and a modest reduction in the same layers of area 32. Neurogranin is one of the intracellular proteins which is found inside dendritic spines and cell bodies. The researchers suggested that their results confirmed the loss of dendritic spines in the prefrontal cortex (Broadbelt et al. 2006).

According to a neuroimaging study utilizing functional MRI (fMRI) (Krug et al. 2013), homozygote carriers of the neurogranin gene mutations displayed abnormal brain activity while performing an episodic memory encoding and retrieval task. The study showed differential brain activation in the anterior cingulate cortex during encoding and posterior cingulate regions during retrieval. These areas are associated with episodic memory processes, and impaired function in these regions has been observed in individuals with SCZ (Krug et al. 2013).

A longitudinal MRI study comparing healthy controls and patients with SCZ found a significant reduction in whole brain volume, especially in the prefrontal cortex (Figure 2) (McIntosh et al. 2011). The authors reported that volume reduction in this brain area is mainly due to the loss of gray matter, especially in the DLPFC (McIntosh et al. 2011). The study also showed a 10% reduction of gray matter in layer III of DLPFC in patients with SCZ compared to healthy age and gender-matched controls.

Multiple underlying mechanisms have been suggested to play a role in the pathophysiology of dendritic spine abnormalities in this area. The expression levels of CDC42 effector protein-3 (CDC42EP3) were significantly increased in patients with SCZ, which is suggested to be involved in assembling septin filaments in dendritic spine necks (Glausier and Lewis 2013). Based on current research, it appears that when glutamate is stimulated, CDC42 is activated, which in turn leads to the inhibition of CDC42EP3 activity. This then causes the complex of septin filaments in dendritic spine necks to dissociate, ultimately allowing molecules such as cytoskeletal proteins and second messengers to move from the parent dendrite and promote synaptic potentiation (Glausier and Lewis 2013).

When a decrease of CDC42 occurs concomitantly with a CDC42EP3 up-regulation, septin barriers in the dendritic spine and neck become less permeable. This leads to a decreased response to glutamate reduction by reduction of the molecular influx, reducing entrance of the molecules involved in the dendritic spine plasticity (Rho GTPases, neurotrophins, calmodulin, and calmodulin-dependent protein kinase-2) (Joberty et al. 2001). Studies have documented that specific molecules, including CDC42 effector protein-4 and PAK3 mRNA, increase in DLPFC layer III.
neurons. These molecules play a role in regulating CDC42 (Ide and Lewis 2010).

Myristoylated alanine-rich protein kinase C substrate (MARCKS) is another gene that regulates the actin cytoskeleton in dendritic spines. An increase in MARCKS mRNA expression levels is reported in both schizophrenia and bipolar disorder patients compared to healthy controls (Konopaske et al. 2015). It has been shown that dysbindin-1, a regulatory protein of MARCKS, is present in high levels in the DLPFC of patients with SCZ (Konopaske et al. 2015). It is believed that dysbindin-1 has a negative correlation with the length of basilar dendrites and the number of dendritic spines per basilar dendrite. Basal dendrites are an essential part of the dendritic tree in pyramidal neurons. This ultimately leads to a reduction in the amount of synaptic surface area in individuals with SCZ (Kolluri et al. 2005; Konopaske et al. 2018).

Other than dendritic spine density, dendritic measures, including morphology, elasticity, number, and function, are intact in deep layers five and six pyramidal neurons in the prefrontal cortex of patients with SCZ, according to Kolluri et al. (Kolluri et al. 2005). However, unlike Kolluri et al., Glantz and Lewis have shown decreased dendritic spine density in prefrontal cortical neurons in schizophrenia. The authors demonstrated that the dendritic spine loss in the DLPFC is seen in pyramidal cells in deep layer III (Glantz and Lewis 2000).

Many macro- and microscopic abnormalities have been reported in the temporal cortex of patients with SCZ (Figure 2) (Talbot et al. 2011). The main results include temporal lobe volume loss and shrinkage of its medial structure. Microscopic alterations described in patients with SCZ include a reduced dendritic spine number and density (Talbot et al. 2011).

It has been found that while dysbindin in the DLPFC remains stable, patients with schizophrenia exhibit a specific decrease in dysbindin-1A in the superior temporal gyrus ( McKinney et al. 2017). McKinney et al. reported that these alterations in the dendritic spine (reduced number and density) were correlated with significantly higher DNA methylation in the temporal gyrus of patients with SCZ compared to healthy controls (McKinney et al. 2017).

In the hippocampus and the respective brain circuit of patients with SCZ, abnormalities in dendritic spines and smaller brain volumes, have been observed in both micro- and macroscopic evaluations, especially in the early stages of the disease (Figure 2) (Kolomeets et al. 2005; Talbot et al. 2011; Tamminga et al. 2010).

Moreover, reductions in dendritic spine volume fraction, invaginated dendritic spine number, spine size, and alterations in dendritic arborization were reported in patients with SCZ with predominantly positive symptoms (Stepan et al. 2015). Also, the number of dendritic spines (per mossy fiber) in the synapses between mossy fibers – axonal terminals of hippocampal dentate granular cells – and dendrites of pyramidal cells in the stratum lucidum of hippocampal CA3 were reduced (Stepan et al. 2015). These synapses play a crucial role in the trisynaptic circuitry which consists of parallel loops connecting the hippocampus to neocortical regions that contribute to memory and spatial learning. Unfortunately, patients with SCZ often experience deficits in these cognitive abilities (Stepan et al. 2015). Similar dendritic arbor neuropathologies have been reported in subjects with bipolar disorder as well as patients with SCZ (Konopaske et al. 2014). Moreover, in this line, significant biological relatedness between schizophrenia and bipolar disorders has been documented (Clementz et al. 2016).

Similar findings were observed in the stratum radiatum in CA3, showing that in this area the apical dendritic spines have a higher density and the number of thorny excrescences is increased (Law et al. 2004). Interestingly, spinophilin-a dendritic spine marker – was significantly down-regulated in hippocampal formation. However, as opposed to the auditory cortex, Law and colleagues observed no reductions in the expression of MAP2 protein in the hippocampus (Law et al. 2004). Similar to the findings in the superior temporal gyrus, dysbindin-1B and 1C were reduced in the hippocampal formation of SCZ patients (McKinney et al. 2017).

Dendritic spine morphogenesis in pyramidal neurons depends on the function of the Rac1 guanine nucleotide exchange factor kalirin-7 (Ma et al. 2003). In a case report, Russel and colleagues (Russell et al. 2014) identified a rare coding variant in the region of the KALRN gene called DI1338N in one patient with SCZ and his sibling, who suffered from a major depressive disorder. This variant inhibited the elevation of dendritic spine size and density and reduced the catalyzation of Rac1 activation (Russell et al. 2014).

Matrix metalloproteinase 9 (MMP-9) is another factor involved in the normal morphogenesis of dendritic spines and synaptic plasticity. Lepeta et al. showed that MMP-9 rs20544 C/T single-nucleotide polymorphism (SNP) located in the 30 untranslated regions (UTR), is associated with chronic delusional syndrome (Lepeta et al. 2017). They also observed an alteration in dendritic spine morphology among the impaired synaptic activity of MMP-9, which was affected by the rs20544 SNP.

In another study conducted by Mckinney et al., brain-specific, angiogenesis inhibitor 1-associated protein 2 (BAIAP2) and discs large homolog 1 (DLG1) were identified
as two genes involved in the dendritic spine density abnormalities (McKinney et al. 2017).

Similar to the regions mentioned earlier, an increased density of cortical-type synapses in the caudate matrix and putamen patch was observed by Roberts et al. in SCZ patients on typical antipsychotic drugs (Roberts et al. 2005). They suggested that these abnormalities impair synaptic pruning and cause abnormal connectivity and limbic or cognitive dysfunction.

The immune system’s involvement in SCZ has been suspected for many years. Recent research on complement C4 has been linked to an increased risk of developing SCZ, and some of these risk alleles affect C4 expression in the brain. C4 is expressed by neurons and can be found in axons, dendrites, and spines/synapses. Its role is in synapse elimination, and these risk alleles can result in synapse engulfment by phagocytic microglia, resulting in accelerated synaptic elimination (Sekar et al. 2016). These results demonstrate that excessive complement activity is involved in the development of abnormal brain circuits and behavior in SCZ (Sellgren et al. 2019), and may help explain the reduced numbers of synapses in the brains of individuals with SCZ (Yilmaz et al. 2021).

3 Autism spectrum disorders (ASD)

ASD is a neurodevelopmental disorder affecting 1% of the world population. ASD is characterized by impairment of social interactions and communication. Patients with ASD often have restricted and repetitive interests or behaviors. Some patients display unique cognitive profiles, including challenges in social cognition and perception and executive and information-processing functions that differ from the norm (Lai et al. 2014; Vahia 2013).

Although genetic factors play the main role in the neurobiology of ASD, environmental factors have also been known to contribute to the disease. Genes regulating the plasticity of synapses play an essential role in ASD etiology through protein synthesis, synaptic transmission, actin cytoskeleton function, and chromatin remodeling (Bourgeron 2015; Nickl-Jockschat et al. 2012; Nickl-Jockschat and Michel 2011a,b).

Dendritic spine abnormalities play an important role in ASD pathophysiology in different ways; higher dendritic spine density has been found in the cortical pyramidal cells of patients with ASD compared to unaffected individuals, which is significantly increased in layer II of the frontal, temporal, and parietal regions and layer V of the temporal lobe (Figure 4) (Hutsler and Zhang 2010).

Patients with ASD with poorer cognitive functions showed even higher dendritic spine density causing changes in the cerebral cortex connectivity and leading to cortical processing difficulties (Weir et al. 2018). In addition, lower brain weight was associated with high dendritic spine densities in these patients (Weir et al. 2018).

Cerebral magnetic resonance imaging studies (Pereira et al. 2018; Sato and Uono 2019) demonstrated reduced connectivity between the white matter of parietal, frontal, and temporal lobes in patients with ASD compared to healthy individuals. This effect was especially pronounced around the ventromedial prefrontal cortex and superior temporal sulcus. Furthermore, white matter tracts linking the amygdala to the neocortex showed reduced integrity. These changes relate to impairments in social awareness and empathy (Pereira et al. 2018; Sato and Uono 2019).

Furthermore, Weir et al. (2018) found that patients with ASD showed a marked elevation of dendritic spine density in the amygdala during development than in healthy controls (Figure 4). Dendritic spine density remains unchanged in a healthy aging brain, whereas in ASD brains, it declines progressively as they age. Therefore, no differences are found in the dendritic spine densities of healthy and ASD brains in adulthood. These findings suggest a different amygdala development pattern in ASD. This might be essential in these patients’ previously described impaired amygdala function (Pereira et al. 2018; Sato and Uono 2019). Interestingly, in children, the amygdala volume is higher in the ASD group than in healthy children (Weir et al. 2018).

MRI studies of the amygdala in patients with ASD showed a reduced volume of gray matter, reduced cortical thickness, weakened functional connections with the ventromedial prefrontal cortex, and decreased overall activity (Sato and Uono 2019). Another study showed that cortical thickness reduction and gray matter loss were correlated with the severity deficits in social skills deficits (Pereira et al. 2018). Moreover, reduced activity in the amygdala was associated with impairment in demonstrating emotional facial expressions (Ciaramidaro et al. 2018).

Several studies have investigated molecular mechanisms that might explain dendritic spine pathology in ASD. Pacault et al. (Pacault et al. 2019) reported a de novo gene deletion in a male patient with autism and intellectual disability. A deletion in the 2q37.2 locus spanned 1Mb and included the AGAP1 and SH3BP4 genes. AGAP1 is shown to be expressed in the developing stages of the brain and is involved in the formation of dendritic spines and synapse function. It also is involved in endosomal trafficking along with SH3BP4. Their results show a possible causative effect of these genes on the disability of the patient (Pacault et al. 2019).
Additionally, individuals with ASD exhibit decreased cortical thickness and loss of gray matter over time in the fusiform gyrus (Sato and Uono 2019). These changes ultimately result in reduced cortical activity that corresponds with cortical dysfunction, as evidenced by MRI studies (Sato and Uono 2019). Nicolini et al. (2015) reported down-regulation of the Akt/mTOR pathway and the proteins involved, including full-length TrkB, PI3K, Akt, phosphorylated and total mTOR, p70S6 kinase, eIF4B, and PSD-95 in the fusiform gyrus of patients with ASD. This pathway regulates dendritic spine formation and function as well as synaptic plasticity; thus, mutations in these genes adversely affect dendritic spine characteristics and synaptic function (Nicolini et al. 2015).

Spinelli et al. (2015) studied germline mutations in the phosphatase and tensin homolog deleted on chromosome ten (PTEN) in patients with ASD. PTEN is a phosphatase involved in the suppressing function of the class I phosphoinositide 3-kinase/AKT signaling pathway. They demonstrated that although AKT suppression remains intact in PTEN mutations, most expressed PTEN proteins are unstable, contributing to soma size suppression and reduction in dendritic spine density and length in primary neurons (Spinelli et al. 2015). Also, research on the cerebral organoids derived from patients with ASD indicates that Pyk2, a calcium-dependent non-receptor protein-tyrosine kinase belonging to the focal adhesion kinase (FAK) family, plays a significant role in dendritic spine structure and synaptic function, and its expression varies in organoids derived from individuals with ASD (Ilieva et al. 2022).

Evaluation of proteomic phenotypes of these cerebral organoids showed differentiated expression levels of 10 proteins including Rac1/cdc42, similar to patients with SCZ, as reported by Ilieva et al. (2022).

Zhao et al. (2019) investigated missense variants in patients with ASD and found eight de novo missense POGZ variants in these patients. POGZ is one of the cardinal genes involved in mitosis, and its missense variants are found in neurodevelopmental disorders. Furthermore, they observed cellular localization of POGZ due to two inherited missenses, making it unable to repair the neurite defects and impairments in dendritic spine developments caused by POGZ knockdown (Zhao et al. 2019).

As seen in patients with SCZ, MMPs contribute vastly to the pathogenesis of ASD. According to Abdallah and Michel (Abdallah and Michel 2013), MMPs affect ASD brains through their essential roles in neuroinflammation, disruption of the blood-brain barrier, and regulation of cytokines, chemokines, and neurotrophic factors (NFs). As such, Nickl-Jockschat and Michel (2011a,b) have emphasized the importance of NFs in ASD pathogenesis by showing alterations in the serum levels of various NFs.

Brain-derived growth factors are a group of NFs involved in the regulation of neuronal development and
spine morphogenesis (Nickl-Jockschat and Michel 2011a,b). The reduced level of this factor is related to ASD-susceptible genes, suggesting another route for the progression of spine pathology in these populations (Nickl-Jockschat and Michel 2011a,b).

4 Alzheimer’s disease

AD is a progressive neurodegenerative disorder with a prevalence rate of 155 million, worldwide. The clinical symptoms manifest with memory dysfunction and cognitive impairment, leading to behavioral impairment and mortality. However, the disease process starts much earlier before the clinical symptoms surface (van Oostveen and De Lange 2021).

There are different hypotheses about the underlying pathology of AD. In the so-called amyloid cascade hypothesis, abnormal deposition of amyloid-β protein contributes to the formation of senile extracellular plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau aggregates (van Oostveen and De Lange 2021).

Numerous imaging studies show widespread atrophy in multiple brain regions. The hippocampal formation is an area well studied in this context. The atrophy is related to disease progress and the development of more severe symptoms. Other than the above-mentioned notions, ventricular expansion is also described (Cardenas et al. 2011). A positron emission tomography (PET) study using the synaptic vesicle glycoprotein 2A (SV2A) in patients with AD reported a significant loss of synapses in the hippocampus (Cai et al. 2019).

Mijalkov et al. (2021) found that dendritic spine loss in AD happens in clusters, and tau accumulation determines the formation of these clusters within neurons (Figure 5), leading to the loss of dendritic spines. Interestingly, abnormal tau phosphorylation is discovered in a specific dendritic spine subset, placed on the hippocampal CA3 neurons shaping as thorny excrescences. Mossy fibers (axons of granule cells) form synapses with these abnormal spines, leading to memory impairment in patients with AD (Blazquez-Llorca et al. 2011).

Neuman et al. (2015) investigated alterations in axon-spinous synapses in CA1 pyramidal neurons of the hippocampus (Figure 5). They detected putative compensatory alterations in the synapse strength between proximal and distal dendrites, implying more robust and powerful numerous synapse boutons of patients with AD than healthy controls (Neuman et al. 2015).

Structures resembling α-amylase, a salivary enzyme that breaks down food polysaccharides, are found in synapses. According to the literature, it is suggested that this enzyme leads to the degradation of glycogen present in the synapses, resulting in memory formation (Byman et al. 2018; Duran et al. 2013, 2019; Perry et al. 2007). Alpha (α)-amylase gene (AMY1A) is found in the normal dendritic spines. Byman and colleagues studied post-mortem hippocampal tissue samples and reported a higher risk of progressing AD in patients with lower amounts of AMY1A copy number, whereas, in patients with high amounts of α-amylase activity, the hazard ratio versus healthy controls was significantly lower (Byman et al. 2020).

Drebrin is another dendritic protein downregulated in patients with AD, according to Julien et al. (2008), who studied post-mortem brain sections of patients with AD and controls. Drebrin is an actin-binding protein specific to neurons, involved in the morphogenesis of dendritic spines. Its mRNA expression is downregulated in AD, leading to the progression of the disease (Figure 5).

Boros et al. defined a linear relationship between dendritic spines of the DLPCF neurons and age, APOE ε4 allele status, AD pathology, and mini-mental state examination (MMSE) (Boros et al. 2019). They observed an elevation in the dendritic spine length, filopodia density, and a reduction in the diameter of thin dendritic spine heads in patients with AD (Figure 5). Moreover, they discovered an inverse correlation between aging and dendritic spine density.

A decrease in the diameter of the dendritic spine head is associated with higher scores on the MMSE (Boros et al. 2019), which is a tool widely used for screening cognitive function on a global level. Finally, APOE ε4 allele presence, the most critical risk factor of late-onset AD, increased dendritic filopodia and caused alteration in the dendritic spine morphology (Boros et al. 2019).

Moreover, in an FDG-PET study of patients with AD, hypometabolism in the two ventromedial prefrontal regions, including the anterior cingulate cortex and the subgenual areas, was observed (Fouquet et al. 2009).

Dendritic spine density reductions and abnormal morphology of dendritic spines have also been reported in the mammillary bodies’ nuclei in early AD (Figure 5) (Baloyannis et al. 2014). In addition to that, neuron loss and dendritic arbor down-regulation were observed in these patients (Baloyannis et al. 2014). The same findings were reported in the hypothalamic nuclei, including the suprachiasmatic, supraoptic, and paraventricular nuclei (Baloyannis et al. 2015). Also, many abnormally shaped dendritic spines and axons were found in the supraoptic and paraventricular nuclei in patients with AD compared to healthy-aged controls (Baloyannis et al. 2015). Similarly, in the entorhinal cortex, researchers found alterations in dendritic spine length in patients with clinical and preclinical AD (Walker et al. 2023).
It is interesting to note that between 30 and 50% of individuals with AD pathology never become symptomatic in their lifetime. Boros et al. have demonstrated that dendritic spine plasticity acts as a mechanism of cognitive resilience and protects these individuals from developing dementia (Boros et al. 2017).

5 Discussion and conclusions

As discussed extensively, alterations in dendritic spines’ function and morphology play a crucial part in the neurobiology of several neuropsychiatric and neurological disorders. Various alterations happen in dendritic spines during the pathogenesis of these conditions. Patients with SCZ demonstrate a reduction in dendritic spine density and numbers, while patients with ASD show an increased number of dendritic spines along with damaged dendritic spine plasticity. A reduced number and density of dendritic spines are also seen in patients with AD, similar to SCZ; however, morphological changes in dendritic spines are only seen in this population.

Furthermore, the brain regions where dendritic spine alterations occur differ among these three disorders. As eluded, dendritic spines are primarily affected in Brodmann’s areas 41 and 42 of the primary auditory cortex in SCZ, hippocampus in AD, and amygdala in ASD.

The introduction of dendritic spines and the subsequent studies on dendritic spine alterations in neuropsychiatric and neurological disorders (Penzes and VanLeeuwen 2011; Taneja and Ganesh 2021; VanLeeuwen and Penzes 2012) opened a new avenue to study them as a vital factor in the pathogenesis of various diseases.

First, it is essential to better understand the disorder’s pathophysiology in order to develop and devise new and more sophisticated methods to tackle the disease. As such, studies in the past decade show that dopaminergic neurons are key insulin receptors (Kleinridders et al. 2015), and since dopaminergic terminals interact with and support dendritic spines (Penzes et al. 2011; Schultz 1998), insulin resistance in the brain may inhibit dopaminergic neurotransmission (mainly through aging), leading to spine loss.

Secondly, a comprehensive study of the pathophysiology of a disorder enables us to pinpoint and focus on the particular genes and sequences implicated in the advancement of the disease. This knowledge helps us to identify individuals who may be genetically predisposed to the illness, even during prenatal stages.

Third, microscopic changes in the disease process (such as oxidative stress leading to alterations in the expression of neurotropics), tend to happen before the disease causes more severe alterations. Hence, detailed imaging techniques such as molecular imaging with small resolutions to detect dendritic spine changes at the outset...
of the disease process, can lead to early diagnosis and intervention. The imaging of dendritic spines has advanced significantly since the first imaging using Golgi staining by Golgi and the introduction of dendritic spine morphology by Cajal. Currently, high-resolution 2- and 3-dimensional views of dendritic spines are possible, allowing for the examination of their nano-diameter properties (Mancuso et al. 2013).

Additionally, recent advances have allowed researchers to study dynamic dendritic spine morphology and function in real-time, using in vivo techniques such as intravital two-photon or optical fiber microscopy (Mancuso et al. 2013; Shao et al. 2021). Electron microscopy imaging has revealed dendritic spines’ morphology, dynamics, and plasticity (Hotulainen and Hoogenraad 2010). Non-invasive in vivo imaging and synaptic density quantification have become essential tools for early detection, staging, and prognosis of dendritic spine-related diseases; PET imaging of synaptic vesicle glycoprotein 2A (SV2A) has been developed as the first-in-class noninvasive method to measure synaptic density in vivo (Finnema et al. 2016).

Fourth and probably the most important, recognizing dendritic spine pathologies throughout the pathogenesis of multiple disorders has opened new venues for developing novel therapeutic agents targeting molecules involved in dendritic spine pathology in genetically susceptible patients (Penzes and VanLeeuwen 2011). These agents may target the prevention of symptom onset, progression of the disease, improvement of the symptoms, or rehabilitation after the full manifestation of the disorder (Penzes and VanLeeuwen 2011). For instance, emphasizing the important role of oxidative stress in spine pathogenesis (Thorsen et al. 2022), ISRIB, a drug-like small molecule, inhibits the integrated stress response (ISR). ISR develops throughout aging and leads to age-related brain alterations. ISRIB functions by restoring dendritic spine density, thus inhibiting cognitive decline in geriatric populations (Krukowski et al. 2020). SPG101 is another small molecule that improves dendritic spine density and cognitive memory in mouse models of AD. It also enhances dendritic spine plasticity and functional outcomes in rat brain trauma models (Song et al. 2014; Zhang et al. 2019). Similarly, collapsin response mediator protein-2 (CRMP2) improves dendritic spine maturation and memory deficits in AD and brain trauma mouse models (Sun et al. 2020). Therefore, a promising number of spine-targeting small molecules are being developed.

Furthermore, it has been shown that inhibiting Rho-associated coiled-coil containing protein kinases (ROCK2-LIMK1) pathway which mediates Aβ-induced spine degeneration and neuronal hyperexcitability in individuals with AD pathology, using pharmacologic inhibition of LIMKI may provide dendritic spine resilience to Aβ and therefore may benefit cognitively normal patients that are at high risk for developing dementia (Henderson et al. 2019; Swanger et al. 2016).

In summary, considering that dendritic spines serve as the synaptic strength storage site and help transmit electrical signals to the neuron’s cell body, in this review, we summarized the literature regarding dendritic spine pathology in the three disorders with cognitive dysfunctions: schizophrenia, autism spectrum disorders, and Alzheimer’s disease. We also attempted to collect current knowledge on the pathologic pathways leading to dendritic spine pathology, the genes involved, and the proteins in charge of the alterations.

Research ethics: Not applicable.
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**Bionotes**

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