

Review

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Posted Date: 30 June 2023

doi: 10.20944/preprints202306.2231.v1

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Review

Attention Deficit-Hyperactive Disorder (ADHD): from Abnormal Behavior to Impairment in Synaptic Plasticity

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Abstract: Attention Deficit-Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder with high incidence in children and adolescents characterized by motor hyperactivity, impulsivity, and inattention. MRI-based evidences support that neuroanatomical abnormalities as the volume reduction of neocortex and hippocampus are shared by several neuropsychiatric diseases as schizophrenia, autism spectrum disorder and ADHD. In addition, it is well documented the abnormal development and postnatal pruning of dendritic spines of neocortical neurons in schizophrenia, autism spectrum disorder and intellectual disability. A recent report using the prenatal nicotine exposure murine model of ADHD support a delay in spine maturation in CA1 neurons correlated with impaired working memory and hippocampal long-term potentiation (LTP). *In vivo* spine imaging show that dendritic spines are dynamic structures exhibiting Hebbian and homeostatic plasticity triggering intracellular cascades involving glutamate receptors, calcium influx and remodeling of F-actin network. The LTP-induced insertion of postsynaptic glutamate receptors is associated to the enlargement of spine head and long-term depression (LTD) to the spine shrinkage. In this review, we summarize recent evidence emerged from meta-analysis of brain imaging data from ADHD patients, risk loci from global genome-wide analysis and new reports focused on spine molecular structure and dynamics using *in vivo* imaging in neocortex and hippocampus.

Keywords: neurodevelopmental disorders; hippocampus; long-term potentiation; dendritic spines; prenatal nicotine exposure model

1. Introduction

Attention Deficit-Hyperactive Disorder (ADHD) is a neurological disorder with a high incidence in children associated to decreased levels of dopamine and norepinephrine in the brain. The current pharmacotherapy is based in the long-term administration of stimulants as methylphenidate and amphetamine and nonstimulants as atomoxetine inhibiting the dopamine and norepinephrine transporters. ADHD is considered as a neurodevelopmental disorder as Autism Spectrum Disorder (ASD) and schizophrenia (CZ) based in early studies of postmortem brain samples and current data from brain magnetic resonance imaging (MRI), showing decreased volumes in subcortical areas and neocortex [1,2]. It is well known that molecular machinery involved in synaptic transmission is enriched in the dendritic spines, corresponding to small protuberances emerging from dendritic shaft. These structures are remodeled during Hebbian and homeostatic plasticity events modifying

the synaptic strength [3]. The onset of symptoms associated to ASD, CZ and ADHD coincides with the peak of cortical spinogenesis occurring between late childhood and early adolescence [4]. This data supports a neuroanatomic basis for these pathological states associated to alterations in dendritic spine maturation. Several experimental approaches such as *in vivo* high-resolution microscopy, electrophysiology and optogenetics has allowed to study the activity-dependent remodeling of dendritic spines during synaptic plasticity processes in pyramidal neurons of neocortex and hippocampus [5,6]. Recently, several large-scale correlation analyses of neuroimaging and genetic data emerged from the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium have allowed to identify singularities and shared neuroanatomical alterations in neurodevelopmental and neuropsychiatric disorders as ASD, CZ and ADHD [7].

2. Attention Deficit-Hyperactive Disorder (ADHD)

ADHD is a neurodevelopmental disorder with high prevalence (around 5%) among children worldwide characterized by hyperactivity, inattention and/or impulsivity affecting learning and sociability at school [8]. Among non-genetic factors involved in the causation of this disorder figures the maternal smoking during pregnancy and exposure to environmental contaminants have been reported [9,10]. Further, it is known that around 60-70 % of patients exhibiting ADHD during childhood maintain the symptoms in adult age and can co-exists with psychiatric disorders as depression and anxiety [8]. In the 40-60% of children with ADHD the disorder persists into adulthood [11] and also exhibit co-occurrence with psychiatric disorders [12,13].

Several neuroanatomical studies support the view that ADHD is a neurodevelopmental disorder. It has been reported a significantly lower cortical thickness (most prominent in the prefrontal cortex, PFC) in children with ADHD evaluated by brain MRI. The fitting of curves of thickness values obtained by repeated scanning at ages between 7-13 years old children show a delay of ≈ 3 years to attain the peak thickness between healthy and children with ADHD [14]. By another part, the meta-analysis of neuroimaging data obtained in children, adolescents and adults with ADHD show a statistically significant reduction (referred to control groups) in cortical thickness, cortical surface area and volume of subcortical areas such as accumbens, amygdala, caudate, putamen and hippocampus, only in children with ADHD. Interestingly, the only brain area significantly reduced in later stages is the hippocampus in adolescents [15]. In addition, analysis of magnetic resonance imaging data from 145 groups of patients crossing six psychiatric disorders including ADHD reveal a shared profile of difference in cortical thickness [16]. It is noteworthy that the cross-disorder correlation analysis shows a positive value for differences in cortical thickness and gene expression between ADHD and MDD. Recently, it has reported a positive correlation between a neuroanatomical parameter such as gray matter volume in neocortex and basal ganglia and the individual scores in N-back task (to evaluate working memory) in ADHD adolescents [17].

Extensive evidence supports a polygenic origin of ADHD with additional environmental risk factors [18]. A recent genome-wide analysis has uncovered 12 significant risk loci in ADHD. The biological activities in these loci include neuronal differentiation (FOXP2), glutamate receptor trafficking and anchorage to postsynaptic density (SORCS3), regulation of dopamine transporter trafficking (DUSP6) and axon guidance (SEMA6D) [19]. By another part, a familial ADHD has been recently reported caused by a missense mutation in *CDH2* gene coding for the adhesion protein N-cadherin involved in synaptogenesis [20]. Knock-in transgenic mice carrying this mutation exhibit behavioral and cognitive phenotypes associated to ADHD. In addition, CA1 pyramidal neurons contained in brain slices from these animals display a lower frequency of spontaneous miniature excitatory postsynaptic currents (mEPSC) without changes in amplitude of currents, suggesting changes at the presynaptic level. Further, *CDH2*-KO mice exhibit lower levels of tyrosine hydroxylase (TH) transcripts (qPCR) with a significant reduction of TH-positive neurons (immunohistochemistry analysis). These results together with the reduced dopamine concentration in PFC of mutant mice support the effect of N-cadherin mutation on activity levels of dopaminergic pathways and its relevance for ADHD-associated neurophysiology.

ADHD is associated to disfunction of dopamine and noradrenergic systems involving cortical areas as PFC (dorsolateral and ventromedial), cingulate cortex and basal ganglia as nucleus accumbens, caudate nucleus and putamen, affecting neural networks driving executive control, motor function, reward processing and decision-making [21]. The pharmacological therapies approved by the American Food and Drugs Administration (FDA) for the treatment of ADHD include stimulants such as amphetamines and methylphenidate (MPH) and non-stimulants as atomoxetine (ATX). Amphetamines and MPH increase synaptic levels of dopamine and norepinephrine by inhibiting DAT and NET symporters and whereas ATX selectively inhibits NET [22]. Considering drug efficacy and tolerability, the evidence emerged from a network meta-analysis supports as first-choice medication the use of methylphenidate in children and adolescents, and amphetamines in adults [23]. Among non-genetic factors involved in the development of ADHD are the maternal smoking during pregnancy and exposure to environmental contaminants as lead and pesticides [9,10]. Several animal models of ADHD such as zebrafish, mice and rats have been developed allowing the study of cellular and molecular mechanisms underlying the action and efficacy of newly generated drugs for the treatment of the disorder [24]. Rodent models of ADHD can be grouped into three types: genetic models like the SNAP-25 KO mice, DAT KO mice and Lphn3 KO mice and rats, those induced by exposure to environmental chemicals such as lead and pesticides, and by prenatal exposure to nicotine or alcohol [25]. The prenatal nicotine exposure (PNE) murine model exhibits several symptoms described for ADHD patients such as increased locomotor activity, low performance in cognitive tests, inattention, and transmissibility until the third generation. In addition, PNE mice exhibit a reduction of dopamine turnover in frontal cortex and striatum and a significant volume reduction in cingulate cortex [26–30].

3. Long Term Potentiation and ADHD

Excitatory transmission at glutamatergic synapses involves the activation of two types of glutamate-gated ionotropic receptors producing excitatory post synaptic currents (EPSCs). Glutamate released into synaptic space activates the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) present at the postsynaptic membrane allowing the influx of sodium and calcium ions shifting in the resting potential to more positive values. This change in membrane potential relieves the magnesium block of the highly Ca^{2+} -permeable N-methyl-D-aspartate receptors (NMDAR) triggering the activation of Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) and PKC-dependent intracellular cascades. High frequency stimuli trigger LTP involving the insertion of new AMPAR into the spine membrane increasing the synaptic efficacy [31]. AMPARs in the postsynaptic membrane exists as homo or heterotetramers conformed by two subunit types as GluA1, GluA2 or GluA3. In the basal state, AMPA receptors are present in the post-synaptic density of dendritic spines mainly as GluA1;GluA2 and GluA2;GluA3 heteromers. GluA1;GluA1 homomers are translocated to the postsynaptic membrane after a high-frequency stimulation. GluA2-containing AMPA receptors show linear I-V relationship and are Ca^{2+} -impermeable. By contrast, receptors lacking GluA2 subunit are Ca^{2+} -permeable and exhibit inward rectifying currents due to the block with intracellular polyamines at positive potentials. During LTP, the process of translocation and fusion of AMPARs-containing vesicles involves the phosphorylation of residues as Ser831, Ser845 and Ser818 of the GluA1 subunits of receptors. The shift in membrane potential of postsynaptic neurons relieving the magnesium-dependent block of NMDARs allows the calcium influx through receptors activating CaMKII and PKC, inducing the phosphorylation of residues Ser831 and Ser818 of AMPARs, respectively [31,32]. The phosphorylation of Ser845 residues by PKA has been implicated in trafficking of receptors-containing vesicles during LTP and is increased by the activation of adrenergic receptors-dependent pathway [33,34]. After translocation and fusion of AMPAR-containing vesicles to the extrasynaptic membrane and they are mobilized by lateral diffusion to the post-synaptic density and anchored by the scaffold protein PSD-95 and transmembrane AMPARs regulatory proteins (TARPs) [35]. The current model proposed for high frequency stimulus (HFS)-induced hippocampal LTP involves an early phase associated to exocytosis

of receptors-containing vesicles to the extrasynaptic membrane domain and further, the late phase to the lateral diffusion of receptors to the post-synaptic density [36].

Analyzing the effect of MPH on learning and hippocampal LTP at molecular level it has been reported that a single oral administration of MPH enhances hippocampal LTP and improves visuo-spatial learning (evaluated in the Morris Water Maze test) in rats. This effect was associated to increased levels of GluA1-containing AMPARs at the cell surface, and higher levels of phosphorylated receptors at S845 and S831 residues. In addition, whole-cell recordings in CA1 neurons show higher amplitude of EPSCs and enhanced short-term plasticity associated to a lower decay time of currents during 20 Hz stimulation protocols [37]. Taking in account these results supported with pharmacological studies, we proposed a model for the action of MPH of hippocampal LTP in which the drug-induced increase of noradrenaline levels at the synaptic space activates dopaminergic terminals inducing the activation of D1/D5 receptors on the postsynaptic CA1 glutamatergic neurons and the downstream activation of protein kinase A (PKA) in the dendritic spine. This cascade determinates a higher fraction of PKA-induced phosphorylation of GluA1-containing AMPARs at S845 by PKA, increasing the surface levels of receptors and synaptic efficacy of CA3-CA1 circuit. In addition to the HFS-induced increase in the number of AMPARs (LTP_N) at the postsynaptic membrane, a novel mechanism involving a PKA-dependent increase of unitary conductance of AMPARs (LTP_γ) has recently reported [38].

Between symptoms associated to ADHD are the working memory impairments in children [39]. However, little is known about neurophysiological basis of this memory deficit. By another part, the analysis of the dopamine levels in different brain areas by PET based in the competition between endogenous agonist and a synthetic radio ligand of D2/D3 receptor show that MPH administration decrease the labeling in the hippocampus in lower magnitude in ADHD patients compared to healthy controls. These data suggest a lower MPH-induced release of dopamine in hippocampus supporting an under activation of dopamine pathway in this brain area [40]. Recently, using the PNE murine model of ADHD it has been reported that the defect in working memory is associated to a significant impairment in LTP of CA3-CA1 hippocampal synapse. In addition, the whole-cell patch clamp recordings of AMPA- and NMDA-dependent of evoked EPSCs in CA1 pyramidal neurons show a significant reduction of AMPA current amplitude in PNE animals compared to control CA1 neurons. The analysis of the biophysical properties of AMPAR EPSCs in PNE neurons suggest a change in the subunit composition of synaptic AMPARs to an enhanced fraction of GluA2-containing receptors, explaining the lower rectification index of AMPAR EPSC compared to control neurons. The electrophysiological data are supported by Western blot analysis showing that surface GluA1 subunit levels are decreased in CA1 neurons contained in slices from PNE mice, associated to lower levels of phosphorylated GluA1 subunit in residues S845 and S831 in CA1 neurons induced by LTP protocol. These changes were not observed in PNE mice treated with a single administration of MPH [26].

4. Dendritic Spines and ADHD

Several human neurodevelopmental and neuropsychiatric disorders as ASD, SZ and ADHD are associated to abnormal development and maturation of dendritic spines in the neocortex including changes in the pruning phase occurring during late childhood and early adolescence [3]. Dendritic spines are dynamic structures mainly associated to excitatory synapses exhibiting changes in density, morphology and functionality during fetal and postnatal development and activity-dependent remodeling events [41]. The time course of spinogenesis during fetal and postnatal development in humans and rodents (PFC and hippocampus) can be described by three phases: spine density increases and maturation until early childhood, spine density decreases during adolescence (associated to activity-dependent spine pruning or elimination) and stabilization in adulthood [3]. Dendritic spines have been classified in three to five different types as long-thin, thin, filopodia, stubby and mushroom according to the morphological criteria, head diameter and neck length and associated to different states within the spine maturation process [41]. Filopodia type spines are highly dynamic structures present mainly during early postnatal development and almost absent in the adult brain exhibiting lifetimes from minutes to hours. The mushroom type displays mature and

larger structures being the most abundant spine type in the adult brain with lifetimes as long as one year. From *in vivo* two-photon imaging, it has been estimated lifetime values for dendritic spines between hours, days and several months in pyramidal cells of visual cortex [42–44]. Although the classification of spines in different subtypes (between two or five types) considering morphological parameters is generally accepted [41], a recent analysis emerged from high-resolution EM images and 3D spine reconstruction, showing the unimodal and continuous distribution of spine parameters as head volume and neck diameter suggesting the lack of defined morphological subtypes of spines [45].

Using single spine stimulation with uncaged glutamate in hippocampal slices cultured transfected with Enhanced Green Fluorescent Protein (EGFP) and whole-cell patch clamp recordings it has been documented that spine volume and AMPA currents are directly correlated. Small new spines contain low AMPA-dependent EPSCs and bigger persistent spines exhibit higher AMPA-EPSCs. In this cell model, NMDA-dependent EPSC are not significantly different in spines of different size and lifetime [46]. A recent molecular analysis of spine dynamics using high-resolution fluorescence microscopy, electron microscopy and quantitative biochemistry in cultured hippocampal neurons shows that the proteome of mushroom spines are better associated to synaptic strength compared to stubby spines [47].

The intracellular cascade involved in the structural and functional remodeling of dendritic spines during processes of synaptic plasticity have been studied mainly by investigating the effect of knock-out or block of specific proteins over the induction of LTP or LTD [48]. In basal conditions, the proteins involved in synaptic transmission are clustered in postsynaptic densities whereby scaffold proteins as PSD95 allow the anchorage of membrane receptors, auxiliary subunits, kinases, and phosphatases [49]. The high frequency activity-triggered modification of ionotropic GLURs distribution by exocytosis and lateral diffusion triggered by calcium increase induces the polymerization of F-actin filaments inducing the spine head enlargement. LTP-induced spine enlargement (also known as structural LTP, sLTP) involves NMDAR-mediated calcium increase, CaMKII activation, downstream activation of small GTPases (such as RhoA, Ras, Cdc42 and Rac1) leading to the fast remodeling of F-actin [50]. The F-actin dynamics based in polymerization/depolymerization equilibrium is controlled by the interaction with cofilin-1 during the activity-induced spine remodeling [51].

5. Dendritic remodeling and learning

The studies focused on the maturation, homeostasis, and regulation of dendritic spines in mammalian brain have been obtained mainly in neocortex restricted by the limited resolution of microscopic tools for imaging of deep brain structures such as the hippocampus. Early studies were focused on mapping the sensitivity to uncaged glutamate of CA1 pyramidal neurons contained in slices suggest that mushroom-type spines structures are associated to a high density of AMPAR-dependent EPSCs – by whole-cell recording - reflecting functionally mature spines [52]. Using the same experimental approach, they reported that repetitive uncaging glutamate or repetitive stimulation of Schaffer collateral fibers induce a transient enhancement of spine head supporting a structural basis for LTP [53].

The recent development of improved tools of two photon (2p)-microscopy has allowed to study the spine dynamics *in vivo* in long-term imaging in the hippocampus supporting a higher turnover compared to the neocortex. The mathematical modeling of spine kinetics in CA1 pyramidal neurons supports a single spine population with a medium lifetime of ~10 days in the hippocampus, in contrast to the long-(up to several months) and short-(~4 days) lifetime populations described in somatosensory and motor neocortices [6]. In addition, the opposite effect of the NMDAR blocker MK801 on spine density in hippocampal (increase in spine elimination) and cortical neurons (decrease in spine loss) suggest different molecular mechanisms involved in spine dynamics in these two brain areas [6]. The comparative analysis of molecular pathways involved in hippocampal and cortical LTP support different mechanisms undelaying the synaptic plasticity in these areas. LTP

induced in the visual cortex is abolished by PKA inhibitors, in contrast to the hippocampal LTP that is sensible only during postnatal development [54].

The intracellular pathways involved in the sLTP involve NMDAR opening, high increase in cytosolic Ca^{2+} , Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) activation, Ras/RhoA/Rac1/Cdc42 activation, actin filaments polymerization and spine head enlargement. On the other hand, the molecular events associated to LTD involve NMDARs, calcineurin (a Ca^{2+} /calmodulin-dependent phosphatase), cofilin, F-actin remodeling and spine shrinkage. Recently, the local autophagy-mediated degradation of synaptic proteins during chemically-induced LTD in cultured hippocampal neurons has been also involved [55].

The intracellular cascade involved in spine enlargement induced by repetitive stimulation with uncaged glutamate involves activation of AMPA receptors, spine depolarization, NMDA receptor-dependent calcium influx, activation of Ca^{2+} /calmodulin and F-actin remodeling inducing the growth of spine head [53]. The glutamate-induced increase of spine head volume has an initial transient component followed by a long-lasting component. The two phases are inhibited by AP5 (NMDAR specific blocker) and only the sustained phase by KN62 (CaMKII blocker) and fully abolished by latrunculin A (inhibitor of actin polymerization).

The activation of CaMKII during LTP has been directly demonstrated by FRET measurement at single spine level in hippocampal neurons transfected with a CaMKII α labeled with donor and acceptor fluorophores in N- and C-terminals of the enzyme [56]. The LTP induced by pairing two-photon glutamate uncaging and postsynaptic depolarization (by whole-cell patch clamp) of a pyramidal neuron can trigger the transient (and localized) activation CaMKII and increase of the volume of stimulated spines. This activation is dependent of L-type voltage-sensitive calcium channels and is abolished by BAPTA dialysis in the whole-cell configuration, suggesting that calcium nanodomains near calcium channels are sufficient to activate CaMKII in spines and dendrites.

The canonical view of excitatory synaptic transmission involves the calcium-dependent neurotransmitter release from the presynaptic terminal inducing depolarization of postsynaptic neuron triggering the calcium-dependent spine enlargement. Interestingly, following SNARE assembly-associated vesicular fusion by FRET in cultured hippocampal slices, it has been reported that 2P glutamate uncaging-induced spine enlargement enhance the presynaptic exocytosis [57].

Several studies demonstrate a significant spine enlargement and formation of new spines in cortical neurons induced by motor skill learning in mice [58,59]. Fu and coworkers, analyzing the spine dynamics in layer 5 pyramidal neurons of motor cortex by *in vivo* two photon-microscopy have shown that acquisition of motor skills is associated to generation of new spines organized in clusters [60]. This training-induced clustered spine fraction (15.8%) exhibits a significantly larger lifetime and increases in head diameter compared to those non-clustered new spines. The direct relationship between spine remodeling and learning-associated synaptic plasticity became clear from *in vivo* experiments investigating the effect of optogenetically induced shrinkage of task-potentiated spines on motor memory. Hayashi-Takagi and coworkers reported that artificially induced spine shrinkage by selective photoactivation of a Rac1 variant in active synapses is able to erase the acquired motor learning in a rotarod task [61]. Conversely, it has been reported that the increase in stability of newly formed spines in motor cortex enhances motor learning, analyzing the spine dynamics and learning behavior in the PirB (Paired Immunoglobulin Receptor B) knock-out mice [62]. This effect is explained by the requirement of PirB receptor protein-expressed in hippocampal and cortical pyramidal neurons- for NMDA-dependent spine shrinkage in motor cortical neurons. In addition, the motor learning-induced spine remodeling found in motor cortex has been also documented in emotional learning and memory processes. Recently, Xu et al. reported that during fear conditioning occurs spine elimination in the apical dendrites of layer 5 pyramidal neurons of motor cortex. By contrast, during the fear extinction period occurs the formation of new spines [63].

Several studies support mechanisms of spine remodeling induced by growth factors, hormones and drugs [64]. Analyzing the uncaged glutamate-induced sLTP in cultured hippocampal slices by a fluorescence resonance energy transfer (FRET) assay (between TrkB-eGFP and mRFP1-PLC-mRFP1) and 2p-microscopy to evaluate brain-derived neurotrophic factor (BDNF) signaling activation,

Harward and coworkers reported that glutamate-induced TrkB-PLC activation and spine enlargement are significantly blocked by the presence of an anti-TrkB neutralizing antibody in the assay, suggesting the requirement of endogenous BDNF to the glutamate-induced spine remodeling [65].

In addition, the inhibitory effect of specific blockers of NMDAR (AP5) and CaMKII (CN21) on TrkB activation and increase of spine volume support the role of calcium-induced intracellular cascade involving PKC and the downstream Rac1 activation, triggering the fast remodeling of actin cytoskeleton during the spine enlargement [66]. Using the same cell model, it is known that cycloheximide can abolish the uncaged glutamate-induced spine enlargement, suggesting that protein synthesis is required for fast spine remodeling [67]. An additional processes of spine remodeling involving the contraction of neck length induced by spike-timing dependent potentiation (STDP) in neocortical neurons has been recently reported [68].

The effect of ketamine effect as antidepressant has been proposed to be caused by a release of inhibition of glutamatergic transmission blocking NMDA receptors on GABAergic terminals. The increased glutamate in the synaptic space would activate the BDNF-dependent intracellular cascade and spine growth [69]. The psychedelic drug psilocybin has been also proposed as pharmacotherapy for depression. It increases spine density and spine size in frontal cortex pyramidal neurons evaluated *in vivo* using 2p-microscopy in Thy1-YFP mice. This effect persists as long as one month [70].

Several neuroanatomic studies at cellular level suggest a common neurodevelopmental basis for psychiatric disorders such as ADHD, ASD and schizophrenia including increased or decreased spine density due to abnormal spine pruning during development [71]. Post-mortem analysis of brain slices from schizophrenic patients shows low spine density in dorsolateral PFC neurons probably associated to excessive spine pruning during development [2,72]. Recently, it has been reported that the overexpression of the human variant of C4A (complement component 4) in mice reduces spine density and enhances microglial-dependent synapse engulfment and pruning in medial PFC. In addition, the C4A-overexpressing mice exhibit altered social behavior, anxiety-like phenotype and impairment in spatial working memory, evaluated in three-chambers test, open-field-test and novel Y-maze, respectively [73]. These results support the association of complement system-associated genes and risk of schizophrenia [74]. On the other hand, ASD has been associated to a defective spine pruning in layer V pyramidal neurons. Golgi staining of samples of postmortem human temporal lobes shows a significantly lower rate of decrease of spine density (due to spine pruning) occurring between 2 and 18 years [75] as compared to healthy persons. In addition, the analysis of spine density in the haploinsufficient *Tsc2*^{+/-} mice defective in the mTOR-dependent neuronal autophagy show a deficit in synaptic pruning similar to those found in ASD patients [76].

Until now there are no reports focused on the analysis of spinogenesis during the childhood and adolescence stages in ADHD patients. The analysis of dendritic spine density and morphology in CA1 pyramidal neurons contained in Golgi-stained brain sections of PNE animals shows that hippocampal CA1 neurons from these animals exhibit lower spine density compared to control animals. In addition, there is a significant increase of the fraction of thin spines (immature) and a decreased fraction of mushroom type (mature) referred to the percentage of types of spines in control mice [26]. These results support a delay in the development of hippocampus in PNE mice as has been described for ADHD in humans [14]. Noteworthy, CA1 neurons from PNE mice treated with a single dose of MPH exhibit no significant change in spine density compared to neurons of untreated PNE animals. However, MPH induces a significant decrease in the fraction of thin-type immature spines and a significant increase of the fraction of mushroom-type mature spines, suggesting a fast stimulatory effect on maturation status of dendritic spines of hippocampal neurons.

6. Future Perspectives

Recent efforts to elucidate the molecular and cellular basis of the neuropsychiatric disorders have been focused on the meta-analysis of brain imaging data from worldwide patients and analyzing the effects of mutations and risk factors described in humans using animal models. Basic research in animal models for neurodevelopmental and neuropsychiatric disorders to better

understand the mechanisms underlying these pathological states, and their use in preclinical studies for testing the drug efficacy, continue to be fruitful. However, the remarkable differences of neurocytological organization of the neocortex and neuronal cytoarchitecture between mice and humans, make the studies of neurodevelopmental and neuropsychiatric disorders in murine models restricted in terms of effective translation [77,78]. Comparative single-cell transcriptomic analysis of human and mouse cortical neurons show that sequences encoding for serotonin receptor subunits (HTR3A and HTR3B) are classified between the 10% most divergent genes in terms of expression [79]. By another part, single-cell transcriptomic analysis in macaque and human brain areas during prenatal and postnatal development shows a higher and significant divergency in transcriptional profiles at prenatal and adult stages [80]. The recent development of human organoids derived from stem cells open a new alternative for *in vitro* modeling of diseases, cell therapy and drug development [81]. Using human telencephalic organoids generated from stem cell-derived single neural rosettes Wang and coworkers have analyzed brain organoids carrying a hemizygous deletion of an autism- and intellectual disability-associated gene SHANK3. Patch-clamp recordings show that SHANK3-deficient organoids exhibit neuronal hyperexcitability and whole RNA-seq analysis shows that protocadherin and cadherin-dependent pathways are downregulated. Considering that protocadherin α is considered as a susceptibility gene for ASD, validates this organoid-based *in vitro* system for the investigation of neurodevelopmental diseases as for modeling and further drug development [82].

A relevant unsolved question in Neuroscience is to determinate the neuroanatomical cues involved in the acquisition of higher cognitive functions during the mammals and human evolution. Recently, the presence of an anterior-posterior gradient of retinoic acid in primate brain during development, enriched in PFC and involved in neocortex fetal development, has been reported [83]. Interestingly, the gradient of retinoic acid is absent in the mouse brain. Among the downstream targets of retinoic acid during the neurodevelopment the synaptic organizer CLBN2 (cerebellin family member) was found, whose expression is also enriched in the PFC. *CLBN2* gene contains multiple cis regulation sites of repression mediated by Sox5, explaining the reduced spinogenesis in PFC neurons in rodents. The *CLBN2* gene in humans lacks Sox5 binding sites in two gene enhancers making the expression of this organizer insensitive to inhibition by Sox5 allowing an increased spinogenesis in the PFC, supporting a structural basis for higher cognitive functions in humans [83]. These results contribute to uncover the neuroanatomical cues involved in the acquisition of higher cognitive functions in humans during the primate evolution. In this context, recent studies focused on the development of the neocortex during the recent evolution of Hominidae have been reported. From comparative analysis of genomes of modern human and Neanderthal has been identified a single amino acid substitution in the TLTK1 protein, an enzyme required for fatty acid synthesis. The variant found in modern humans determines the proliferation and growth of basal radial glial cells, progenitors localized in the subventricular zone, mainly promoting cortical neurogenesis in the frontal lobe [84]. Future molecular and cellular biology studies focused to dilucidate the molecular events involved in human brain spinogenesis will be relevant to better understand the origin and progression of neurodevelopmental and neuropsychiatric disorders. By another part, several studies support the influence of extrinsic factors such as diet, stress, and drug consumption during pregnancy on the development of ADHD [18]. Recently, it has been proposed as an epigenetic marker of ADHD the methylation state of DAT gene [85]. Further studies focused in global and gene-specific epigenetic modifications associated to extrinsic factors during prenatal development and childhood as inducers of ADHD will be useful to better understand the molecular basis of these disorders.

Author Contributions: Conceptualization, G.U. and B.M.; draft writing, review and editing, G.U., B.M., R.P., C.R., M.Z., F.G., D.C. and D.R.

Fundings: This work was supported by DICYT grant # 0211843RS (C.R), DICYT grant # 031693Z (M.Z), ANID Fellowship 702350 (F.G), ANID grant # 859968 (F.G), FONDECYT postdoc grant # 3190897 (D.C), DICYT 022343MM_postdoc (B.M), DICYT 021223MMN_postdoc (B.M), grant 5392202MMN-ACDicyt (B.M), and

Dirección de Investigación Universidad Metropolitana de Ciencias de la Educación - Chile grant # 12-2023-SAC (R.P.)

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflict of interest: The authors declare no conflict of interest.

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