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Review Article

Glutamatergic Neurotransmission in ADHD: Neurodevelopment and Pharmacological Implications

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Abstract

Animal models, human genetic and epigenetic studies as well as imaging and functional brain studies lend support for significant glutamatergic dysfunction in ADHD. Furthermore, medications with glutamatergic functions decrease ADHD symptoms and effective ADHD medications have glutamatergic activity. Neurodevelopmental studies indicate that glutamatergic neurotransmission has widespread impact on brain development throughout gestation and after birth. This provides a wide window of vulnerability along the lifeline, where insults such as hypoxic-ischemic injuries, infections, teratogens, genetic and epigenetic factors can disrupt glutamatergic function leading to ADHD symptomatology. No Glutamatergic biomarkers have thus far been identified informing biological processes for ADHD, or other neuropsychiatric disorders. This is not surprising given the wide window of vulnerability impacting on a multitude of glutamatergic functions, and our limited knowledge of the human Central Nervous System (CNS). This, however, is rapidly changing as newer tools such as single cell transcriptomics have recently led to discoveries of new subsets of glutamatergic neurons. Additional tools such as human induced pluripotent stem cells (hiPSC) and derived cortical organoids will further our understanding of the underlying disease mechanisms and this will allow the development of safer and more effective ADHD treatments. Treatments applied during gestation and neonatal periods remain to be developed but have the potential for decreasing morbidity and potentially preventing ADHD and other neuropsychiatric disorders from manifesting.

Key Points

- Animal models, brain imaging and functional studies, human genetic and epigenetic studies as well as pharmacological studies indicate a significant role for glutamatergic dysfunction in ADHD.
- Glutamatergic neurotransmission has widespread impact on brain development throughout gestation and after birth and insults disrupting glutamatergic function during various developmental phases can contribute to ADHD symptomatology.
- Newer tools are rapidly allowing discoveries of the human CNS neurons, circuits, and functions throughout development, and this will likely lead to better treatments and possibly prevention of ADHD.

Introduction

Attention Deficit, Hyperactivity Disorder (ADHD) is a syndrome manifested by symptoms of hyperactivity, impulsivity, inattention and other executive function deficits [1]. Clinically, however, it is much more complex with epidemiological, neuropsychological and genetic twin studies indicating symptoms on the extremes of a continuum [2-4] with inattentive symptoms becoming more apparent in the older children [5,6]. ADHD is highly comorbid with other disruptive behavioral disorders, anxiety and mood dysregulation in children [7,8] and adults [9] as well as neurodevelopmental disorders [10]. Brain imaging and functional studies reflect the clinical complexity. No single brain structure has been associated with ADHD and consistent findings indicate reduced total intracranial volume as well as reduced volumes in a number of sub-cortical anatomical regions including the accumbens, caudate, putamen, amygdale and hippocampus [11] and delays (2.5 to 5 years) in prefrontal cortical thickening [12,13]. *In vivo* neuroanatomic imaging of monozygotic twins discordant for ADHD, identified similar cortical dimensions but smaller right striatum and thalamus and larger cerebellum dimensions in the affected twins [14]. Functional studies consistently indicate hypoactivation in various brain regions during response inhibition tasks(frontal, parietal, thalamic, basal ganglia, cingulate cortex) [15], attention demanding tasks (frontal, basal ganglia, thalamus, parietal and temporal) [15,16], reward anticipation (striatum) [17,18], cognitive tasks, motor timing as well as in resting state (cerebellum) [19,20].

The involvement of numerous brain regions has led to studies examining connectivity using structural and functional measures [21]. Structural connectivity referring to anatomical connections and functional connectivity referring to temporal correlations in neural activity between brain regions. While disruption in various networks are reported in both children [22] and adults [23-25], replication has been difficult due to various methodological issues. In a large, well-done study of ADHD adults with childhood onset, stronger connectivity was reported in the anterior cingulate gyrus of the executive control network and trends in the cerebellum network,

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with considerable overlap in connectivity values between patients and controls [26]. More recent work, using data from "rich-club" organization identified highly connected nodes within brain networks connecting to other nodes in healthy human brains. The "structural" and "functional" rich club regions differed with the former including the superior medial frontal/dACC, medial parietal /PCC, insula and inferior temporal cortex while the latter included midline frontal, midline posterior, insula, inferior temporal and cingulate cortex [27,28]. Using this context, lower levels of structural and functional connectivity inside these "rich-club" regions were found in ADHD youths [29]. Environmental factors such as in-utero drug exposure [30,31], prematurity, low birth weight [5,32], young maternal age and adverse life experiences are associated with increased risk for ADHD. However, the greater risk is due to genes given the high heritability estimates up to 76% [33] and concordance rates of up to 80% and 40% in monozygotic and dizygotic twins respectively [34]. The initial focus for candidate genes included genes involved in dopaminergic and noradrenergic dysregulation, considered to be the main contributors to ADHD pathophysiology [35] with some showing replicable evidence of association [36]. The advent of Genome Wide Association Studies (GWAS), allowing the exploration of the whole genome without apriori hypotheses, led to discoveries of glutamatergic gene variants in ADHD. Copy number variations (CNVs) in glutamatergic receptor genes *GRM5* and *GRM7* were first reported by Elia and colleagues [37] in an ADHD cohort. In a larger cohort (1,013 cases of ADHD and 4,105 controls) that used a two-stage genome-wide association for high-resolution CNV detection, 12 loci showed enrichment of CNV's in ADHD cases compared to control. Four genes belonging to the metabotropic glutamate receptor gene family, *GRM1*, *GRM5*, *GRM7* and *GRM8*, replicated in independent datasets of ADHD (2,493 cases) and controls (9,222) genotyped on matched case-control platforms [38]. Further replications include *GRM5* CNV variants were reported in ADHD cases with anxiety [39] and of the mGluR network genes in an autism cohort, highly comorbid for ADHD [40]. Investigating CNVs and Single Nucleotide Polymorphisms (SNPs) in ADHD, rare and common variant genes involving the glutamatergic synaptic development were reported by Yang and colleagues [41]. Gene network analysis indicate a significant impact of glutamatergic disruption accounting for 10% of cases in one of these studies and 22% in a separate sample of 1876 children and adolescents where CNV-positive subjects had more emotional dysregulation, driven in part by a relatively large number of subjects with *CNTN4* CNVs [42]. Using whole blood DNA from monozygotic twins discordant for ADHD, pathway analyses showed an enrichment of signaling in pathways related to GABA in the affected twins. ADHD animal genetic models also provide supports for significant glutamatergic involvement as noted in Table 1.

Pharmacotherapy

Glutamatergic medications and ADHD effects

NMDA receptors are scattered throughout the brain with greater aggregation in the dendrites of pyramidal cells in the hippocampus and cortex (areas involved in memory, cognition and learning). Chronic low dose administration of NMDAR agonists have been reported to induce apoptosis [43,44] and at high doses have been reported to induce necrosis. In normal conditions, released glutamate is metabolized or taken up by neighboring cells. When pathways are disrupted, glutamate accumulates and overexcites the NMDA receptors. NMDA receptors act as a Ca^{2+} (calcium ion) channel that is activated by glycine, glutamate or NMDA. These channels function only when the cell membrane is depolarized due to the blockade of the channel by Mg^{2+} (magnesium). This prevents the influx of Ca^{2+} when the neuron is at rest. In pathological conditions, the membrane is depolarized chronically, Mg^{2+} leaves the channel and Ca^{2+} influx is unrestricted for longer periods leading to cell death through free radicals [45] or through overload of mitochondria resulting in free radical formation, capsase activation and release of apoptosis-inducing factors [46]. NMDA antagonists decrease the permeability of the channel and prevent an influx of $Ca2^{+}$ providing neuroprotection. Therefore, medications that could block this activity could therefore modulate glutamatergic tone and potentially improve ADHD symptoms. As summarized in Table 2, medications that target glutamatergic hypoactivity have been reported to have some modest effect on ADHD. Amantadine, a glutamatergic antagonist binds to the NMDA receptor and prevents the excessive excitation by glutamate has been shown to be helpful in a number of neuropsychiatric disorders including ADHD [47], Memantine, an analogue of amantadine, likewise been shown to have modest improvement in ADHD in human studies [48]. The ADHD effects however may also be due to

Table 1: ADHD Animal Models and Glutamatergic Function.

Animal Model	Glutamatergic Function
DAT KO	Hyperactivity can be increased by NMDAR blockers and suppressed by drugs that increase glutamatergic transmission [1].
DAT KD	Dopamine transporter expression is reduced to 10% [2] and these animals are in a chronic hyper-dopaminergic state.
	Electrophysiological recordings from medium-sized spiny neurons show alterations in amplitude and frequency of spontaneous glutamate-receptor mediated synaptic currents [3].
DRD4 KO	Extracellular glutamate levels increased in striatum [4].
SNAP-25	Increased levels of extracellular glutamate in hippocampus [5].
NHE	Increased levels of PFC glutamate [6].
	Electrophysiological analyses of hippocampal CA3-to-CA1 synapses show reduced synaptic transmission and reduction LTP by NR2B specific blocker CP-101.606 [7].
SHR	Glutamatergic impact on other neurotransmitters such as increased dopamine has been hypothesized to be due to altered glutamate regulation of dopamine neurons [8].
	The NMDAR antagonist MK-801 increased glutamate-stimulated release of radioactively labeled NE in hippocampal slices and this effect was blocked by CNQX, an AMPA-receptor antagonist [9].
	Dysregulated expression of genes in glutamatergic pathways animal [10-13].
GRM KO	Deletion of (GRM) gene, *GRM5* and inhibition of mGluR protein mGluR5 with a pharmacological antagonist resulted in increased spontaneous locomotor activity in rats [14] and comparable results were obtained with *GRM7* [15] and *GRM8* KO mice [16].

AMPA: amino-3-hydroxy-5-methyl-4-isoxazole propionate; DAT: Dopamine Transporter; DAT KD: Dopamine Transporter Knock Down; DAT KO: Dopamine Transporter Knock Out; DRD4 KO: Dopamine Receptor D4 Knock out; GRM: Glutamate Receptor Metabotropic; KO: Knock out; LTP: Long Term Potentiation; mGluR: metabotropic glutamate receptor; NHE: Naples High Excitability; NMDAR: N-methyl-D-aspartate receptor; PFC: Prefrontal Cortex; SNAP 25: Synaptosomal nerve associated protein 25; SHR: Spontaneous Hypertensive Rat

Table 2: Medications targeting glutamate or glutamate receptors: ADHD effects.

	ANIMAL MODELS	HUMAN ADHD STUDIES
AMANTADINE Weak, non-competitive NMDAR antagonist [1]. Enhances dopamine release indirectly via antagonism of the NMDAR [1,2].		Open study in 9 ADHD children (age 10-13). MPH discontinued for 1 week followed by amantadine treatment for 1 month. Amantadine was rated as intermediate effect between MPH and no meds [3].
		6-week open study in 24 ADHD children (age 5-13). Improvement in ADHD but more modest than stimulants [4].
		D-B, placebo controlled trial in 39 Autistic children (age 5-19). Improvement in hyperactivity [5].
		Over 400 children reported treated with amantadine in book "Delivered from Distraction" [6]
		D-B, 6-week randomized trial of amantadine vs MPH in 40 ADHD children (age 6-14). Improvement in ADHD for both amantadine and MPH with greater improvement for MPH [7].
MEMANTINE (analogue of amantadine) Non-competitive NMDA-R antagonist [8,9].	Memantine, administered 4 hours after initiation of NMDA mediated neurotoxicity in rats, prevented death of neonatal ganglions [10].	8-week open trial in 16 ADHD children (age 6). Improvement in ADHD [11].
	Exposure in rats to low doses of in-vitreal glutamate resulted in 42% loss of retinal cells that was mitigated by memantine [12].	12 week open trial in 34 ADHD adults. Improvement in ADHD [13].
		D-B, 6-week randomized trial of memantine vs MPH in 40 ADHD children (age 6-11). Improvement in ADHD for both amantadine and MPH with greater improvement for MPH [14].
		D-B, placebo controlled, 12 wk memantine added to open label MPH in 12 ADHD adults.
D-CYCLOSERINE Partial agonist at glycine-binding site of NMDARs [16].	D4R K-O mice with viral expression of hD4.4 (normal variant) or hD4.7 (variant associated with ADHD) in PFC were used to examine impact of hD4R polymorphisms on NMDARs and ADHD-like behaviors. Direct stimulation of NMDA-Rs with D-cycloserine prevented the NMDAR hypofunction induced by hD4.7 activation. hD4.7 mice exhibited increased exploratory and novelty seeking behaviors. Treatment with D-cycloserine improved these ADHD-like behaviors by enhancing basal NMDAR-mediated synaptic current in hD4.7 expressing neurons and preventing NMDAR hypofunction induced by hD4.7 activation [17].	None
KETAMINE NMDAR antagonist [18].	Post-natal (Day11) administration of ketamine in male mice pups resulted in initial hypoactivity followed by hyperactivity that was reduced by d-amphetamine. Cell degeneration was noted primarily in parietal cortex [19,20].	None

D-B: Double-Blind; hD4R K-0: human D4 Receptor Knock-Out; hD4.7: human D4.7; MPH: methylphenidate; NMDAR: N-methyl-d-aspartate receptor; PFC: Prefrontal Cortex; Vs: versus; Wk: week

the indirect enhanced dopamine release via antagonism of the NMDA receptor [49,50]. NMDARs have the distinct property in that they require binding of two agonists to be fully functional, namely binding of glutamate to the GluN2 subunit as well as a binding of a separate co-agonist to the glycine site of the GluN1 subunit [51]. NMDARs composed of GluN2A subunits have a high affinity for D-serine while NMDARs composed of GluN2B subunits preferentially bind glycine [52]. Administration of D-serine as a potential therapeutic was noted to be limited since chronic use resulted in desensitization and renal damage led to the search for other potential agonists [53]. The antibiotic D-cycloserine is a partial agonist at the glycine site [54]. Treatment of ADHD with in humans has not been studied however animal models suggest some potential. The gene encoding human D4 receptor (hD4R) has a number of variable repeats [55] with the 4 (hD4.4) and 7(hD4.7) being the most common variants with a global frequency of 64% and 21% respectively [56]. The hD4.7 variant has been associated with ADHD [57] and novelty seeking [58] but the mechanisms are not known. However, D4R activation has been shown to modulate NMDAR trafficking and function [59]. In D4R-KO mice with viral expression of human D4.4 (normal variant) or hD4.7 (variant associated with ADHD), Qin and colleagues [60] showed that treatment with d-cycloserine improved ADHD-like behaviors in hD4.7 expressing mice by enhancing basal NMDAR-mediated synaptic currents in hD4.7 expressing neurons and by preventing NMDAR hypofunction induced by hD4.7 activation. Results suggest that over-suppression of NMDAR function may be the mechanism that the genetic variant hD4.7 results in ADHD symptoms. Increasing the NMDAR signaling could then result in therapeutic improvement. The authors do note that that virally expressed human D4 receptor variants are likely to have higher expression levels than endogenously expressed D4 receptors and this would need to be taken into account in human therapeutic uses of D-cycloserine [60]. Treatment of ADHD youths with ketamine, a non-competitive NMDAR antagonist [61] is not supported by animal models showing apoptotic cell loss and induction of ADHD symptoms in post-natally treated mice pups [62,63]. In a small sample of healthy volunteers ketamine was

shown to alter connectivity by disrupting frontoparietal connectivity [64]. In another small sample of healthy adult male volunteers, sub-anesthetic doses of ketamine were reported to decrease connectivity in auditory and somatosensory networks but increase connectivity in cerebellar and visual networks [65] thus raising the question whether there could be benefits in adult patients with impaired default mode cerebellar networks [66,67].

ADHD medications and Glutamatergic Function

As reviewed by Cortese and colleagues [68], stimulant medications remain the first line treatment for ADHD. In 1999, the *SLC6A3-KO* (DAT-KO) mouse, an ADHD animal model, remains responsive to methylphenidate in spite of the lack of a dopamine transporter [69] put into question the predominant dopaminergic theory of ADHD. This was further challenged when it was shown that hyperactivity in these mice was increased by NMDAR blockers and suppressed by drugs that increase glutamatergic transmission [70]. Increased midbrain *SLC6A3* and *DRD4* expression were reported in rats where glutamate transporter increases were found in the striatum [71] suggesting that decreases in dopamine may alter glutamate signaling. Also, glutamate receptor subunit gene (*GRIN2A*) disruption increased DA and serotonin metabolism in the frontal cortex and striatum of mice, and increased locomotor activity that was reduced by dopamine or serotonin receptor antagonist [72]. As noted in Table 3, the commonly used ADHD medications as well as some medications in development impact on the glutamatergic system as evidenced by animal studies. The dopaminergic activity of norepinephrine transporter inhibitor [77]. However animal studies indicate that it reduces NMDAR subunit 2B protein levels [78] and blocks NMDA-induced membrane currents in cortical and hippocampal neurons [79]. In ADHD subjects, h-MRS studies show normalization of increased glutamatergic tone in frontal and striatal brain regions [80] and decreased glutamatergic activation of dorsal lateral prefrontal cortex (DLPFC) neurons [81]. Guanfacine's ADHD efficacy is attributed primarily to its α-2A agonist activity [82]. Microcircuits of pyramidal cells in layer 3 of PFC are interconnected by NMDA glutamate receptors, located in dendritic spines. Next to these are α-2A receptors, which improve neuron connectivity, coordinating the "signal" to create the working memory and behavioral inhibition, essential for PFC function [83]. Animal data also has shown improved working memory deficits induced by the NMDAR antagonist phencyclidine [84]. Guanfacine improves prefrontal connectivity through modulation of glutamatergic activity including NMDAR and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor [85]. Long-term drinking rats had significant increase in NMDA and AMPA currents compared with alcohol naïve-rats and the in-vivo guanfacine treatment significantly reversed this alcohol-induced dysregulation [86]. Metadoxine, is an ion-pair salt of Vitamin B 6 (pyridoxine), a precursor of pyridoxal phosphate-dependent enzymes that are necessary in the biosynthesis of several neurotransmitters including serotonin, epinephrine, norepinephrine and ϒ-aminobutyric acid (GABA) [87]. Preliminary clinical studies in adults with ADHD treated with metadoxine, have reported efficacy and tolerability [88,89]. Modafinil binds DAT and inhibits DA reuptake [90,91]. Animal models indicate an inhibitory effect on GABA release that is dependent on a catecholaminergic network [92]. ADHD studies indicated efficacy similar to stimulants but FDA approval was not successful due to Stevens Johnsons syndrome [93]. Fasoracetam, modulates adenyl cyclase activity through mGluRs [94-96] and increases $GABA_B$ receptors in rat cortex [97,98]. In an open, single blind, placebo controlled study that included 30 ADHD (ages 12-17) children who also had comorbid anxiety and mood dysregulation andharbored mutations in the mGluR network genes, fasoracetam resulted in significant improvement especially in mGluR Tier 1 variants [99]. In human subjects, Magnetic Resonance Spectroscopy (MRS) studies have shown increased glutamatergic signaling in fronto-striatal pathways, in many but not all ADHD youths [100-104] leading to increased activity at glutamate receptors AMPA and NMDA while decreased signaling has been reported in ADHD adults [105,106]. GABA concentration, measured *in vivo* by edited MRS is reduced in children with ADHD compared to controls [107]. Short intercortical inhibition is modulated by $GABA_A$ agonists [108] and a study using TMS found reduced short intercortical inhibition in ADHD children [109]. Regional GABA concentrations have also been reported to correlate with motor control and impulsivity in healthy adults [110]. In a Single Photon Emission Computed Tomography (SPECT) study of 35 ADHD children using 123I-iomazenil (binds with high affinity to benzodiazepine receptors), higher binding activity was seen in the posterior cingulate cortex suggesting that GABAergic inhibitory neurons may be playing a significant role [111]. As noted in Table 4, in humans ADHD MRS studies this increased glutamatergic tone in frontal and striatal brain regions normalizes with stimulants and atomoxetine [112] but not in a subsequent study. MRS studies also indicate that methylphenidate could lead to increased activity of glutamatergic pathways by the dopamine reuptake inhibition in mesocortical areas or a direct effect on NMDA glutamatergic receptors.methylphenidate [73] and amphetamine [74,75] are well known and considered to be the main pathways of conferring efficacy in ADHD. However animal models show various effects of these medications on glutamatergic functions in various brain regions, some effects being dose dependent [76]. Atomoxetine's efficacy in ADHD is attributed primarily to its activity as a selective

Glutamatergic CNS Neurodevelopment

In the human embryo the neocortex is first recognized at 6 weeks post conception and is fully established by 7 weeks post-natally [113] with ontogenic events orchestrated in specific space-time sequences. The human CNS contains 86.1 billion neurons [114], 16.3 billions of these estimated to be localized the outer 2 to 3 millimeters of the cerebral hemispheres known as the cerebral cortex [115]. About 80% of these cortical neurons are thought to be excitatory glutamatergic projection neurons (pyramidal cells and spiny stellate cells) [116] and the rest are local circuit GABAergic inhibitory interneurons [117-119]. As detailed in Figure 1 by the 5th week (peaking at 8-12 weeks), the earliest neurons to emerge in the human embryonic cortical plate are the GABAergic inter neurons. Other neurotransmitter systems development follows and by the 8th week, 5HT Serotonin Transporter (SERT) antibodies emerge in fibers from the raphe, reach the subplate at week10 and arrive at the cortical plate at week13 [120,121], dopamine like receptors D_1 and D_2 first expressed at 9 to 10 weeks respectively [122] and levels α7 nicotinic acetyl-choline receptor mRNA expression are identified between 9-11 wks [123] Figure 2. The majority of GABAergic inter neurons are generated between 10 and 25 weeks post-conception [124] and consist of two lineages, one originating from the neocortical ventricular and subventricular zone of the dorsal forebrain expresses Dlx1/2 and Mash 1 transcription factors and comprises about 65% of the neocortical GABAergic neurons in the human brain. A second lineage, comprising about 35% of the GABAergic neurons originates from the ganglionic eminence of the ventral forebrain and expresses only DlX1/2. Early in development

Table 3: Animal Models and Glutamatergic Effects of ADHD Medications.

METHYLPHENIDATE DA and NE reuptake inhibitor [1]	DAT1 KO, remains responsive to methylphenidate in spite of the lack of a dopamine transporter [2]. Hyperactivity in these mice can be increased by NMDAR blockers and suppressed by drugs that increase glutamatergic transmission [3].
	Ibotenic acid lesions of glutamate PFC neurons in rats modulated effects of MPH [4].
	In midbrain rat slices MPH and AMPH increased PFC glutamatergic EPSC. However only higher doses of MPH induced NMDAR but not AMPA/kainite receptor mediated EPSC effects. AMPH induced both but effects were greater on AMPA/kainite [5].
	4-week old rats treated with low and high MPH doses showed that at low dose MPH selectively potentiates NMDAR mediated EPSC's via adrenergic receptor activation and also restores NMDAR function in those exposed to stress. High doses MPH suppressed both NMDAR and AMPA mediated EPSC's [6].
AMPHETAMINE Promotes release of DA and NE [7,8].	AMPH increases extracellular glutamate in various brain regions including the striatum, VTA and NAc [9-13].
	AMPH inhibits metabotropic (but not ionotropic) glutamate receptor (mGluR)-mediated IPSPs in DA enhancing phasic release of DA [8].
	Neonatal administration of glutamate receptor antagonists (MK-801, ketamine, ethanol) in mice pups caused hypoactivity followed by hyperactivity that was reversed by d-AMPH [14].
	In midbrain rat slices MPH and AMPH increased PFC glutamatergic EPSC. However only higher doses of MPH induced NMDAR but not AMPA/kainite receptor mediated EPSC effects. AMPH induced both but effects were greater on AMPA/kainite [5].
	AMPH stimulates endocytosis of the excitatory amino acid transporter (EAAT3), in dopamine neurons in vitro and in vivo which increases glutamatergic signaling [15].
	AMPH increases NMDAR-mediated synaptic currents and decreases AMPAR/NMDAR ratios in midbrain DA neurons. This potentiation is dependent on activation of NMDAR-GluN2Bsubunit [16].
ATOMOXETENE **NET inhibitor [17].**	Atomoxetine blocked NMDA-induced membrane currents in cultured rodent cortical and hippocampal neurons [18].
	Decreased levels of NMDAR subunit 2B, and NET were found after atomoxetine treatment. Two months after exposure genes coding for NMDAR subunits and NMDAR protein levels were reduced [19].
GUANFACINE α-2A agonist [20]	Guanfacine improves working memory deficits produced by NMDA-R antagonist phencyclidine [21].
	Hyperactivity in SHR rat reduced by guanfacine [22].
	The PFC has a balance mechanism modulated by α2Areceptors. Low dose guanfacine enhances excitatory impulses through closure of HCN channels, but at high doses attenuates excitatory impulses by inhibiting activation of AMPA receptors [23].
	Guanfacine decreased fEPSP in medial PFC inhibiting excitatory synaptic transmission [24].
	Guanfacine suppresses eEPSC in mPFC pyramidal cells. This inhibition is mediated by Gi-cAMP-PKA-PP1-CaMKII-AMPAR signaling pathway [25].
	Improves prefrontal connectivity by modulating NMDA and AMPA receptors [26].
	Long-term drinking rats had significant increase in NMDA and AMPA currents compared with alcohol-naïve rats and the *in vivo* guanfacine treatment significantly reversed this alcohol-induced dysregulation [27].
METADOXINE Increases synthesis of DA, 5HT [28]	Necessary for synthesis of neurotransmitters including GABA [29].
MODAFINIL (diphenyl methyl sulfinyl acetamide). Binds DAT, inhibits DA reuptake [30,31]	Modafinil treatment in guinea pig produces reduction of GABA outflow. After 6-hydroxy-dopamine treatment, (which depletes catecholamine levels) modafinil fails to inhibit cortical GABA release. The catecholaminergic telencephalic networks seem essential for the elicitation of the inhibitory effects of modafinil on GABA release [32].
	In rodents, modafinil blocks GABA and increases glutamate release in dose-dependent manner in some brain regions such as the cortex, nucleus accumbens and in sleep-related brain areas (medial preoptic area and posterior hypothalamus) medial preoptic area and posterior hypothalamus [33]. In other regions (VMT, VLT and Hippocampus) glutamate was increased but not GABA [34]. In the striatum and palladium, GABA release was inhibited without any changes in glutamate at the lower doses. At the higher doses it further reduced pallidal but not striatal GABA release and increased striatal but not pallidal glutamate release while in the substantia nigra it reduced only GABA release without affecting glutamate release [35].
	Modafinil also impacts on other neurotransmitters. In the *in-vivo* (halothane anesthetized rat) modafinil-induced increase of dopamine release that was associated with a significant reduction of accumbens GABA release [36,37] and in a separate study the reduction of GABA transmission was noted to involve local 5-HT3 receptors [37,38].
FASORACETAM Glutamatergic modulator [39-41].	*In vitro* studies in rat primary cortical neurons, fasoracetam modulates adenyl cyclase activity through mGluRs [39-41].
	In vivo, 14-day administration of fasoracetam increased $GABA_B$ receptors in rat cortex [42,43].

AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; DA: Dopamine; DAT: Dopamine Transporter; DLPFC: Dorsolateral Prefrontal Cortex; EAAT: Excitatory Amino Acid Transporter; EPSC: Excitatory Post-Synaptic Currents; fEPSP: field Excitatory Post-Synaptic Potential; GABA: ϒ-Aminobutyric Acid; HCN: Hyperpolarization-activated Cyclic Nucleotide-gated Channel; IPSP: Inhibitory Postsynaptic Potentials; MPA: Medial Preoptic Area; MPH: Atomoxetine; NMDAR: N-methyl-D-Aspartate Receptor; NAC: Nucleus Accumbens; NE: Norepinephrine; SHR: Spontaneous Hypertensive Rat; VTA: Ventral Tegmental Area

they are primarily excitatory in nature by depolarizing and exciting targeted neurons by an outwardly directed flux of chloride controlled between the cation-chloride importer NKCC1 and the exporter KCC2. Around week 16 post-conception, a differential isoform expression of *KCC2* drives the developmental switch of GABA from excitatory to inhibitory activity [125].

As reviewed by Marin-Padilla in humans pyramidal neurons are the most abundant fundamental cell types of the mammalian neocortex. They originate in the cortex ependymal neuroepithelium and using radial glia ascend to the 1st layer of the neocortex where they remain anchored for life. They are incorporated in the primordial

Table 4: ADHD Medications and GLUTAMATERGIC Activity in Human ADHD Studies.

METHYLPHENIDATE DA and NE reuptake inhibitor [1].	^{1}H-MRS studies have shown increased glutamatergic tone in frontal and striatal brain regions of ADHD subjects [2-5] that normalized with MPH [6] but not in all studies [7,8].
	^{1}H-MRS in 12 ADHD children treated with MPH showed increased glutamatergic signaling in right and left PFC [9].
	^{1}H-MRS in 21 ADHD children before and after 2-month treatment with MPH or Atomoxetine showed MPH increased glutamatergic activation in white matter behind the DLPFC [10].
	GWAS study investigating response to the methylphenidate in ADHD children detected nominal evidence for association of several SNPs including SNPs within *GRM7* [7].
ATOMOXETINE NET inhibitor [12] and NMDAR antagonist [13].	^{1}H-MRS studies have shown increased glutamatergic tone in frontal and striatal brain regions of ADHD subjects that normalized with atomoxetine treatment [3].
	^{1}H-MRS in 21 ADHD children before and after 2 months treatment with MPH or atomoxetine, atomoxetine decreased hyper activation of DLPFC neurons [10].

DA: Dopamine; DLPFC: Dorsolateral Prefrontal Cortex; GWAS: Genome Wide Association Studies; GRM: Metabotropic Glutamate Receptor; ^{1}H-MRS: Magnetic Resonance Spectroscopy; MPH: Methylphenidate; NMDAR: N-methyl-D-Aspartate Receptor; NE: Norepinephrine; NET: Norepinephrine Transporter; PFC: Prefrontal Cortex; SNP: Single Nucleotide Polymorphism

cortex from 8-15 weeks gestation, establishing the neocortex gray matter, where most neurons reside. The pyramidal neurons incorporate additional segments of functional synaptic membrane to its apical dendrites at 15,20,25,30,35 weeks and birth. The ongoing specialization of cortical pyramidal neurons are thought to play a critical role in primate executive cortical functions [126]. The mammalian glutamate receptor ion channels include the ionotropic cation-permeable receptor channels and the G-protein coupled metabotropic glutamate receptors [127,128]. Most, if not all cells in the nervous system, express at least one type of glutamate receptor [129-133] and expression of glutamate receptor subunit mRNA is apparent as early as the 8th week of gestation [134]. Expression of NMDAR in human fetal forebrain peaks during weeks 20-22 [135]. As noted in Figure 1, the NMDAR have 6 subunits. Expression of subunit mRNA was highest for NR1, NR2B and NR2D with increased expression at weeks 11,13 and 19. In normal white matter, the NR1 and NR2B levels were highest in preterm period compared to adults while in gray matter, NR2A and NR3A expression was highest near term [136]. Kainate receptor subunit expression was predominant for KA2 and GluR7 with transient periods of high expression at weeks 11,13 and 19, while AMPAR subunit expression was at low levels for all four transcripts. Migration peaks between weeks 12-20 [137] with GABAergic local circuit neurons migrating tangentially from the telencephalon to diencephalon between 18-36 weeks gestation [138]. The first synapses are formed in the cerebral cortex at 6 to 7 weeks of gestation [139,140]. After formation of the cortical plate, synaptic density increases rapidly and peaks around 24-26 weeks in all cortical regions with peak synaptic density occurring in the visual and auditory cortices around 3 months postnatal and in the prefrontal cortex around 15 months [141]. As reviewed by Ben-Ari [142] GABAergic synapses are formed before glutamatergic synapses. GABAergic interneurons mature first and innervate other interneurons providing most synaptic currents initially and orchestrating the activity of the entire network [143,144]. Axon and dendrite sprouting and synapse formation peak during the last trimester and 1st postnatal year while the major telencephalic myelination occurs during 1st year after birth [145]. The generation of astrocytes coincides with the initiation of synapse formation with the astrocytes contacting immature neurons making them competent to form synapses [146]. This is followed by astrocyte secreted signals that instruct the formation of immature, silent and then mature synapses [147]. Astrocytes also have receptors for multiple neurotransmitters [148] and D-serine, released from astrocytes is a co-agonist for NMDAR through which it regulates synaptic plasticity [148-150]. Glia also regulate neurotransmitter uptake via glutamate transporters. Pre-myelinating oligodendrocytes are present at 17-20 weeks gestation with myelination occurring in the last trimester, first in the basal ganglia and later in the corpus callosum [151-153]. OPCs generate myelinating oligodendrocytes throughout life while mature oligodendrocytes generate myelin sheaths and may impact on ADHD symptomatology since myelinated fibers assemble in bundles, forming large white matter tracts easily detected by MRI and are reduced in ADHD [154,155]. OPCs also control postsynaptic NMDAR and AMPAR-mediated currents and plasticity through cleavage of the transmembrane proteoglycan NG2 [156]. Subtypes of glia with distinct neurogenic and gliogenic potentials are reported and radial glia-derived progenitors persist through adulthood and give rise to adult neural stem cells [157]. Microglia, the brain's resident macrophages, are not derived from neuroepithelium as are the neurons and glia, butdevelop from erythromyeloid progenitors, entering the CNS at the onset of neurogenesis and subsequently proliferate and colonize the brain and spinal cord [158]. Microglia regulate neuronal survival, are involved in synapse formation apoptosis during early development and in neurogenic regions of the adult brain [159]. In addition, they play a major role at the interface between the immune system and CNS [160-162]. Activation of the maternal immune system during pregnancy or early life has been shown to exert long-term effects on the wiring of neural circuits and may contribute to the etiology of neurodevelopmental disorder [163].

Glutamatergic Vulnerability

A number of regional and temporal patterns of vulnerability emerge during glutamatergic neurodevelopment [164,165]. Glutamatergic afferent synapses from almost the entire cortex converge on the striatum, a core structure that has been implicated in ADHD, led Lou to conclude that this area is highly vulnerable to ischemia [166]. Glutamate concentrations in extracellular spaces are low and strictly regulated since an excess release of glutamate can result in excitotoxicity of post-synaptic neurons and cell death [167], hypoxic-ischemic events, common in premature infants might, induced the release of glutamate, damaging this vulnerable structure and conferring risk for ADHD. Lou's hypothesis has been further supported by studies reporting hypoxia impairing the energy dependent glutamate transport, allowing extracellular glutamate to accumulate and initiate excitotoxic neuronal injury and death [168-170]. In a study that generated neurons from human embryonic stem cells, increased responsiveness of neurons to glutamate-induced Ca^{2+} influx was attributable to NMDAR activity that was concomitant with an increase in expression of mRNA encoding NMDA and AMPAR subunits. Differentiated neurons were vulnerable to glutamate excitotoxicity in a dose-dependent manner that was reduced by an

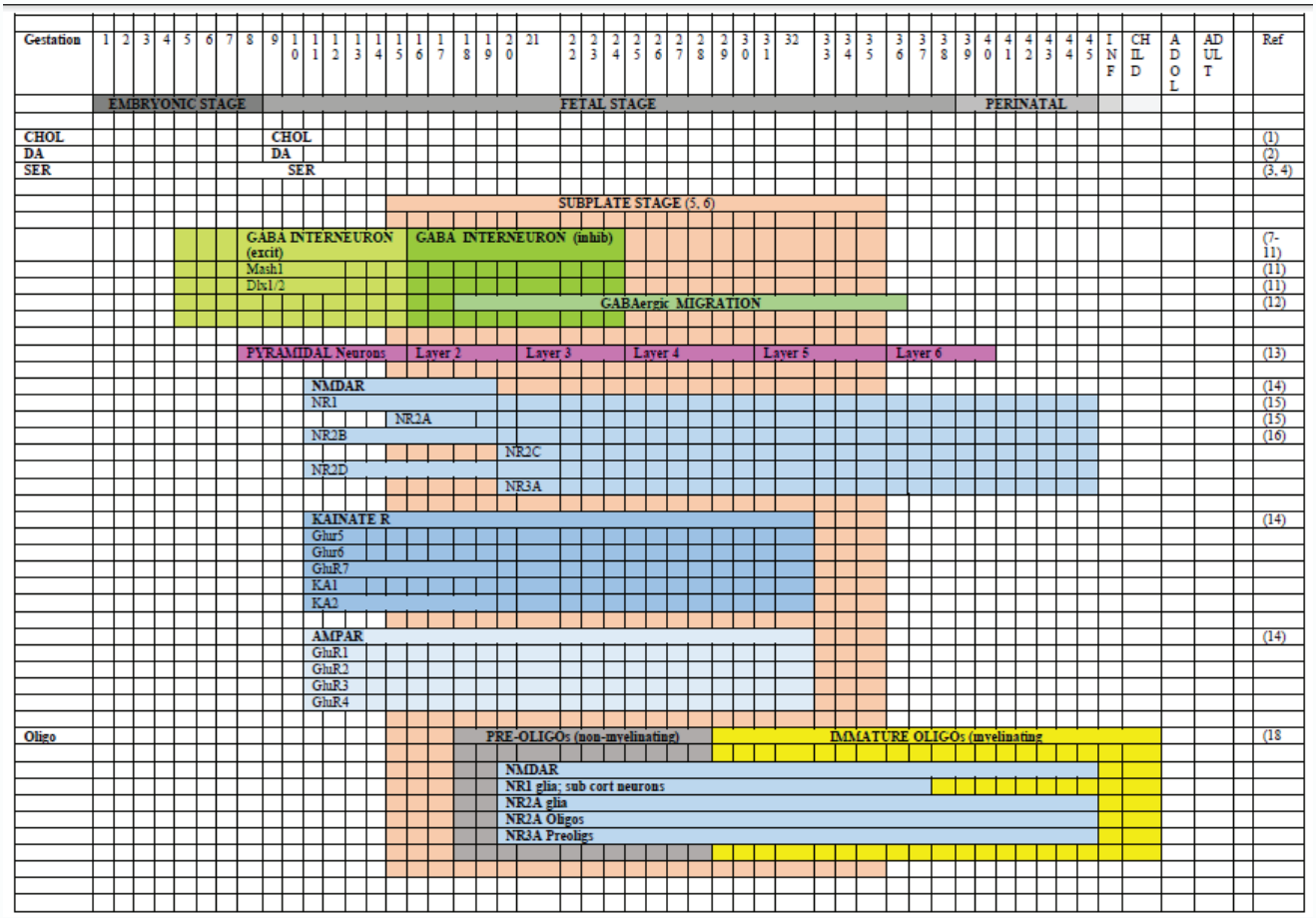

Figure 1: Cortical Glutamatergic Neurodevelopment and Vulnerability.

NMDAR antagonist (+) MK801 [171]. Rats injected with the NMDA antagonist (+) MK801 for only a few hours during late fetal or early neonatal life had widespread neurodegeneration [172]. This effect was not reproduced by blocking other major excitatory systems in the brain (muscarinic, non-NMDA glutamatergic, dopaminergic). The authors hypothesize that many neurons during this critical stage are dependent on glutamate stimulation through NMDA receptors and deprivation of this input activates programmed cell death. This is a window of vulnerability in humans exposed to drugs of abuse prenatally that are potent NMDAR antagonists (phencyclidine, ethanol) [173-175] and for human infants exposed to ketamine [176] and nitric oxide [177], widely used anesthetics. In addition to the inhibition of glutamate uptake by activated microglia resulting in oligodendrocyte excitotoxicity, non-lethal activation of kainite receptors on oligodendrocytes rapidly sensitizes these cells to complement attack as a consequence of oxidative stress. In addition ATP signaling can directly trigger oligodendrocyte excitotoxicity via activation of CA permeable P2X7 purinergic receptors, which mediate ischemic damage to white matter. Blockade of P2X7 receptors attenuates this post-ischemic injury to white matter and ameliorates chronic experimental autoimmune encephalomyelitis. Activating mGluR1 and mGluR5 receptors on developing oligodendrocytes limited white matter injury significantly in a rat model of periventricular leukomalacia. *In vitro* studies show that activation of group 1 mGluRs with ACPD or DHPG (3,5-dihydroxyphenylglycine) protected oligodendrocytes from oxygen and glucose deprivation in a rat modelof PVL [178]. The developmental stage however may be critical given that mGluR1 and mGluR5 localization peaks in oligodendrocytes (white matter) whereby at later stages (2nd postnatal week) their expression increases on nonmyelinating glia (microglia and astrocytes). Neuronal expression of mGluRs is also lower during peak mGluR expression in oligodendrocytes. ACPD treatment did not increase seizures, most likely because f the low expression of mGluR's on neurons at this stage. As reviewed by Thion and colleagues [179], systemic inflammation during pregnancy has been associated with defective brain wiring with animal studies implicating cytokine IL-6 and IL-17 in the deleterious effects of prenatal inflammation [180]. In a mice models, maternal immune activation (MIA) is thought to cause these deleterious effects though its impact on microglial dysregulation of a subset of cortical inhibitory interneurons [181], and disruption of microglial developmental trajectories [182]. In humans, IL-6 levels in pregnant mothers have been correlated with functional connectivity and working memory in 2 year old infants [183] while increased risk of neuropsychiatric disorders have been reported in offspring of mothers with bacterial and viral infections during 1st and 2nd trimester [184]. Data from a Danish national registry contradicts this [185] however limitations of data from linked registries [186] and results from maternal immune activation studies point to the potential impact of MIA on neurodevelopment. As reviewed by van Gelder and colleagues [187] with regard to teratogenicity, human

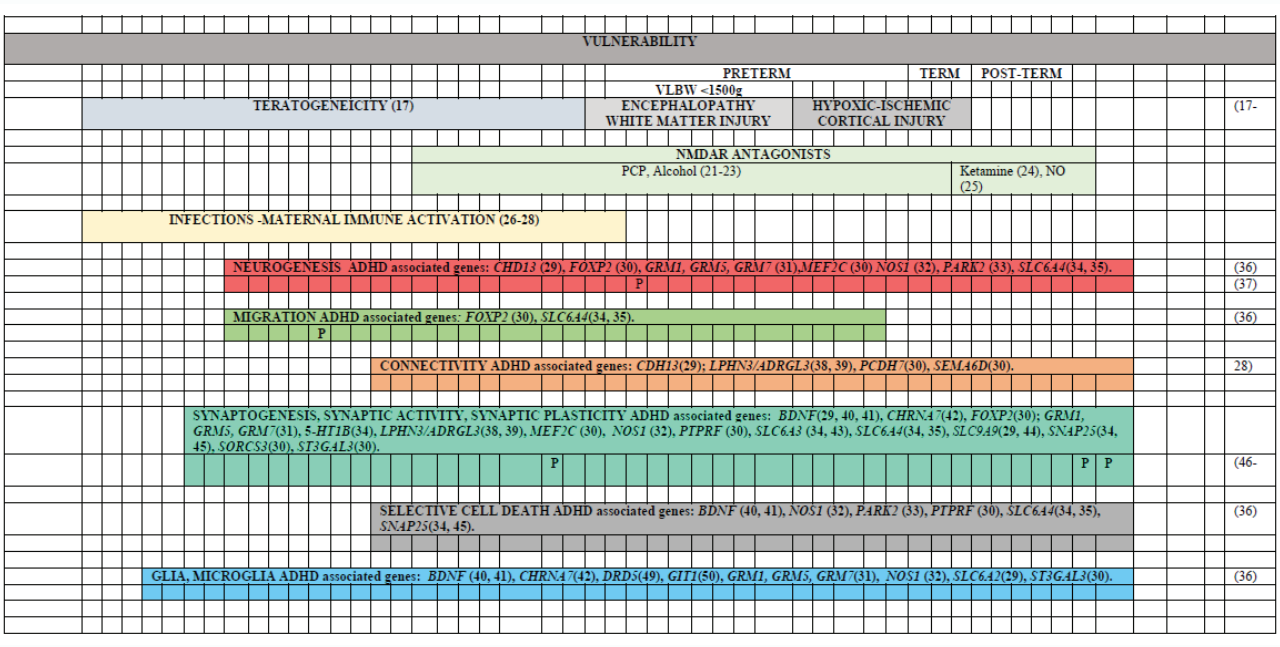

Figure 2: Schematic drawing of glutamatergic cortical development.
GABAergic interneurons, the earliest neurons in the human cortical plate emerge by week 5 (peak 8-12 weeks). By the 8th week, 5HT serotonin transporter (SERT) antibodies emerge in fibers from the raphe, reach the subplate at week10 and arrive at the cortical plate at week13 [3,4], dopamine like receptors D1 and D2 first expressed at 9 to 10 weeks respectively [2] and levels α7 nicotinic acetyl-choline receptor mRNA expression are identified between 9-11 wks [1]. The subplate zone, a transient cortical structure between 13-25 weeks gestation in humans, contains the earliest born neurons, radial glial processes, radially and tangentially migrating neurons, early developing astrocytes and microglia. It provides a "waiting area" for the developing thalamocortial afferents, basal forebrain cholinergic afferents and callosal and ipsilater cortico-cortial afferents, all which head for cortical destination [5,6]. Radial Glia give rise to Gamma-aminobutyric acid (GABA)-ergic interneurons initially form a layer in the subplate zone (a transient cortical structure that exists between 15-35 gestational weeks in humans) [5,6]. GABA neurons are initially excitatory and around the 16th gestational week, the first differential isoform expression of KCC2 drives the developmental switch of GABA from excitatory to inhibitory [10]. Pyramidal neurons 10emerge between 8th and 15th week and attach to the 1st lamina of the neocortex. They then incorporate additional segments of functional synaptic membrane to its apical dendrite at 15, 20, 25, 30, 35 weeks and birth (13 Expression of NMDAR in human fetal forebrain is apparent by the 8th week. Transient periods of high expression reported for NMDA subunits NR1, NR2B, NR2D, Kianate R KA and GluR7 while AMPAR subunits were expressed at low levels [14]. The first synapses are found in the cerebral cortex around 6th to 7th week [47]. Glia includes radial glia, astrocytes and oligo-dendrocytes, the myelin producing cells. Pre-myelinating oligodendrocytes are present at 17-20 weeks gestation with myelination occurring in the last trimester, first in the basal ganglia and later in the corpus callosum [51-53]. The various neurodevelopmental processes present distinct regional and temporal patterns of vulnerability to genetic variations [36], teratogens, infections, insults [18,19], NMDAR antagonists NMDA antagonists [21-25].

AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CHOL: Cholinergic; DA: Dopamine; GABA: Y-aminobutyric acid; mGluR: metabotropic; lutamate Receptor; MPA: Medial preoptic area; NE: Norepinephrine; NMDAR: N-methyl-d-aspartate receptor; P: Peak; SER: Serotonergic; VLBW: Very low birth weight

in-utero exposure to NMDAR antagonists such as amantadine, ketamine, dextromethorphan, does not appear to result in physical teratogenicity. Likewise, benzodiazepine exposure in utero has been implicated in some studies but not others. However there is no data on behavioral or cognitive teratogenicity. During corticogenesis, CB_1R (type 1 cannabinoid receptor) is involved in regulating neural progenitor proliferation, radial and tangential migration of pyramidal cortical neurons and interneurons, axonal path finding and synaptogenesis [188-190]. Prenatal exposure to cannabinoid receptors agonist in rats was reported to be associated with permanent alterations in cortical glutamatergic neurotransmission [191,192]. In a more recent study that limited prenatal exposure to CB_1R and CB_2R (type 2 cannabinoid receptor) agonists during embryonic period in rats, no physical malformations, toxicity or alter gestational parameters were found, however it was found to alter migration of early born GABAergic interneurons and glutamatergic neurons [193]. As reviewed by Dark and colleagues [194] and summarized in Figure 1 and 2 ADHD genes have been associated with all the major phases of neurodevelopment. Interestingly, in monozygotic twins discordant for ADHD, cortical volume did not differ between twins and genes expressed in early cerebral cortical development also did not show differential methylation suggesting that in these ADHD cases the risk conferred for glutamatergic dysfunction is likely post-natal. In mice models with genetic deletions of the glutamate receptors, brain development is normal whereby in mice exposed to excess glutamate due to lack of glutamate transporters (GLAST, GLT1), multiple brain areas are deformed involving stem cell proliferation, radial migration, neuronal differentiation and survival [195]. NR1 deletions in these mice rescued these brain defects [196].

Future Studies

Morphological characterization using slice physiology has been the standard for studying the neocortex in the past [197]. However, recent technological advances in human Pluripotent Stem Cell (hiPSC) technology, are allowing the generation of enriched human neurons and glia under defined conditions that permit study of human neural cells *in vitro* [160,198]. Advances in single-cell transcriptomics has enabled unbiased, high throughput quantitative surveys of

molecularly defined cell types in rodents [199,200] suggesting the presence of several dozen inhibitory and excitatory cell types [199-202]. In the primary visual cortex of adult mice, using single-cell RNA sequencing, 49 transcriptomic cell types were identified, 29 GABAergic, 19 glutamatergic and 7 non-neuronal types. Using single-cell transcriptomics and slice physiology, ten GABAergic interneuron subtypes with combinatorial gene signatures were identified in layer 1 of the human cortex. This is a substantially higher degree of GABAergic neuron complexity in just one layer of the human cerebral cortex (10 types) than what had been previously described in all the cortical layers (8 types) [203]. More recent work using transcriptional dynamics in different classes of interneurons during the formation of cortical inhibitory circuits in mice, the synaptic molecules were found to be expressed in a subtype specific manner [204]. Imaging-based in situ cell type identification and mapping method combined with single-cell RNA sequencing is allowing identification of neuronal populations characterized by distinct neuromodulatory signatures and spatial organizations [205]. The human CNS is much more complex and animal data alone is not adequate. A new type of neuron, thus far only discovered in humans was identified recently. Located in layer 1 of the neocortex it's a GABAergic neuron with a distinct shape and distinct genes are expressed on it. This new GABAergic neuron, thought to play a role in blocking signals from the excitatory pyramidal cells located in deeper neocortical layer [206]. Cortically patterned forebrain organoids, generated from fetal fibroblasts-derived (hiPSC) were found to pattern to forebrain on both transcriptome and regulatory levels, mimicking the longitudinal development of embryonic and early human fetal cortical development [207].

Summary

Given the glutamatergic system's widespread impact on brain development and function, from embryogenesis through adulthood, it is not be surprising that there are significant temporal and spatial windows of vulnerability where risk for ADHD can occur. Treatments include ADHD medications that modulate glutamatergic activity. Preventive interventions in animal studies, such as treatment with NMDAR blockers may mitigate some of the neuronal damage, however applying these strategies to humans is not yet applicable. However, recent technological advances, applied to studying the human brain, including hiPSC, single-cell transcriptomics, imaging-based in situ cell type identification and mapping method combined with single-cell RNA sequencing, are rapidly expanding our understanding of brain development that will likely lead to safer interventions as well as prevention.

References

1. Association AP. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. 5th ed. Arlington Virginia: American Psychiatric Association; 2013.
2. Polderman TJ, Derks EM, Hudziak JJ, Verhulst FC, Posthuma D, Boomsma DI. Across the continuum of attention skills: a twin study of the SWAN ADHD rating scale. J Child Psychol Psychiatry. 2007;48(11):1080-7.
3. Lubke GH, Hudziak JJ, Derks EM, van Bijsterveldt TC, Boomsma DI. Maternal ratings of attention problems in ADHD: evidence for the existence of a continuum. J Am Acad Child Adolesc Psychiatry. 2009;48(11):1085-93.
4. Larsson H, Anckarsater H, Råstam M, Chang Z, Lichtenstein P. Childhood attention-deficit hyperactivity disorder as an extreme of a continuous trait: a quantitative genetic study of 8,500 twin pairs. J Child Psychol Psychiatry. 2012;53(1):73-80.
5. Galéra C, Côté SM, Bouvard MP, Pingault JB, Melchior M, Michel G, et al. Early risk factors for hyperactivity-impulsivity and inattention trajectories from age 17 months to 8 years. Arch Gen Psychiatry. 2011;68(12):1267-75.
6. Egger B, Gold KS, Brand AH. Notch regulates the switch from symmetric to asymmetric neural stem cell division in the Drosophila optic lobe. Development. 2010;137(18):2981-7.
7. Elia J, Ambrosini P, Berrettini W. ADHD characteristics: I. Concurrent co-morbidity patterns in children & adolescents. Child Adolesc Psychiatry Ment Health. 2008;2(1):15.
8. Takeda T, Ambrosini PJ, deBerardinis R, Elia J. What can ADHD without comorbidity teach us about comorbidity? Res Dev Disabil. 2012;33(2):419-25.
9. Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry. 2006;163(4):716-23.
10. Cristino AS, Williams SM, Hawi Z, An JY, Bellgrove MA, Schwartz CE, et al. Neurodevelopmental and neuropsychiatric disorders represent an interconnected molecular system. Mol Psychiatry. 2014;19(3):294-301.
11. Hoogman M, Bralten J, Hibar DP, Mennes M, Zwiers MP, Schweren LSJ, et al. Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. Lancet Psychiatry. 2017;4(4):310-9.
12. Almeida LG, Ricardo-Garcell J, Prado H, Barajas L, Fernández-Bouzas A, Avila D, et al. Reduced right frontal cortical thickness in children, adolescents and adults with ADHD and its correlation to clinical variables: a cross-sectional study. J Psychiatr Res. 2010;44(16):1214-23.
13. Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci U S A. 2007;104(49):19649-54.
14. Chen YC, Sudre G, Sharp W, Donovan F, Chandrasekharappa SC, Hansen N, et al. Neuroanatomic, epigenetic and genetic differences in monozygotic twins discordant for attention deficit hyperactivity disorder. Mol Psychiatry. 2018;23(3):683-90.
15. Dickstein SG, Bannon K, Castellanos FX, Milham MP. The neural correlates of attention deficit hyperactivity disorder: an ALE meta-analysis. J Child Psychol Psychiatry. 2006;47(10):1051-62.
16. Hart H, Radua J, Nakao T, Mataix-Cols D, Rubia K. Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. JAMA Psychiatry. 2013;70(2):185-98.
17. Scheres A, Milham MP, Knutson B, Castellanos FX. Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder. Biol Psychiatry. 2007;61(5):720-4.
18. Suskauer SJ, Simmonds DJ, Fotedar S, Blankner JG, Pekar JJ, Denckla MB, et al. Functional magnetic resonance imaging evidence for abnormalities in response selection in attention deficit hyperactivity disorder: differences in activation associated with response inhibition but not habitual motor response. J Cogn Neurosci. 2008;20(3):478-93.
19. Vloet TD, Gilsbach S, Neufang S, Fink GR, Herpertz-Dahlmann B, Konrad K. Neural mechanisms of interference control and time discrimination in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2010;49(4):356-67.
20. Tian L, Jiang T, Wang Y, Zang Y, He Y, Liang M, et al. Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. Neurosci Lett. 2006;400(1-2):39-43.
21. Castellanos FX, Proal E. Large-scale brain systems in ADHD: beyond the prefrontal-striatal model. Trends Cogn Sci. 2012;16(1):17-26.
22. Fair DA, Posner J, Nagel BJ, Bathula D, Dias TG, Mills KL, et al. Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2010;68(12):1084-91.
23. Wang X, Jiao Y, Tang T, Wang H, Lu Z. Altered regional homogeneity patterns in adults with attention-deficit hyperactivity disorder. Eur J Radiol. 2013;82(9):1552-7.
24. Cubillo A, Halari R, Smith A, Taylor E, Rubia K. A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with Attention Deficit

Hyperactivity Disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. Cortex. 2012;48(2):194-215.

25. Hoekzema E, Carmona S, Ramos-Quiroga JA, Richarte Fernández V, Bosch R, Soliva JC, et al. An independent components and functional connectivity analysis of resting state fMRI data points to neural network dysregulation in adult ADHD. Hum Brain Mapp. 2014;35(4):1261-72.

26. Mostert JC, Shumskaya E, Mennes M, Onnink AM, Hoogman M, Kan CC, et al. Characterising resting-state functional connectivity in a large sample of adults with ADHD. Prog Neuropsychopharmacol Biol Psychiatry. 2016;67:82-91.

27. Grayson DS, Ray S, Carpenter S, Iyer S, Dias TG, Stevens C, et al. Structural and functional rich club organization of the brain in children and adults. PLoS One. 2014;9(2):e88297.

28. van den Heuvel MP, Sporns O. Rich-club organization of the human connectome. J Neurosci. 2011;31(44):15775-86.

29. Ray S, Miller M, Karalunas S, Robertson C, Grayson DS, Cary RP, et al. Structural and functional connectivity of the human brain in autism spectrum disorders and attention-deficit/hyperactivity disorder: A rich club-organization study. Hum Brain Mapp. 2014;35(12):6032-48.

30. Banerjee TD, Middleton F, Faraone SV. Environmental risk factors for attention-deficit hyperactivity disorder. Acta Paediatr. 2007;96(9):1269-74.

31. Han JY, Kwon HJ, Ha M, Paik KC, Lim MH, Gyu Lee S, et al. The effects of prenatal exposure to alcohol and environmental tobacco smoke on risk for ADHD: a large population-based study. Psychiatry Res. 2015;225(1-2):164-8.

32. Heinonen K, Räikkönen K, Pesonen AK, Andersson S, Kajantie E, Eriksson JG, et al. Behavioural symptoms of attention deficit/hyperactivity disorder in preterm and term children born small and appropriate for gestational age: a longitudinal study. BMC Pediatr. 2010;10:91.

33. Larsson H, Chang Z, D'Onofrio BM, Lichtenstein P. The heritability of clinically diagnosed attention deficit hyperactivity disorder across the lifespan. Psychol Med. 2014;44(10):2223-9.

34. Levy F, Hay DA, McStephen M, Wood C, Waldman I. Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. J Am Acad Child Adolesc Psychiatry. 1997;36(6):737-44.

35. Del Campo N, Chamberlain SR, Sahakian BJ, Robbins TW. The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. Biol Psychiatry. 2011;69(12):e145-57.

36. Gizer IR, Ficks C, Waldman ID. Candidate gene studies of ADHD: a meta-analytic review. Hum Genet. 2009;126(1):51-90.

37. Elia J, Gai X, Xie HM, Perin JC, Geiger E, Glessner JT, et al. Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes. Mol Psychiatry. 2010;15(6):637-46.

38. Elia J, Glessner JT, Wang K, Takahashi N, Shtir CJ, Hadley D, et al. Genome-wide copy number variation study associates metabotropic glutamate receptor gene networks with attention deficit hyperactivity disorder. Nat Genet. 2011;44(1):78-84.

39. Akutagava-Martins GC, Salatino-Oliveira A, Genro JP, Contini V, Polanczyk G, Zeni C, et al. Glutamatergic copy number variants and their role in attention-deficit/hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet. 2014;165B(6):502-9.

40. Hadley D, Wu ZL, Kao C, Kini A, Mohamed-Hadley A, Thomas K, et al. The impact of the metabotropic glutamate receptor and other gene family interaction networks on autism. Nat Commun. 2014;5:4074.

41. Yang L, Neale BM, Liu L, Lee SH, Wray NR, Ji N, et al. Polygenic transmission and complex neuro developmental network for attention deficit hyperactivity disorder: genome-wide association study of both common and rare variants. Am J Med Genet B Neuropsychiatr Genet. 2013;162B(5):419-30.

42. Elia J, Kim C, Khan M, Mazzotti D, Hakonarson H, Anderson C, et al., editors. Glutamatergic Network Gene Mutations in Children and Adolescents with ADHD. 2017 World ADHD Congress; 2017; Vancouver, Canada.

43. Dreyer EB, Zhang D, Lipton SA. Transcriptional or translational inhibition blocks low dose NMDA-mediated cell death. Neuroreport. 1995;6(6):942-4.

44. Bonfoco E, Krainc D, Ankarcrona M, Nicotera P, Lipton SA. Apoptosis and necrosis: two distinct events induced, respectively, by mild and intense insults with N-methyl-D-aspartate or nitric oxide/superoxide in cortical cell cultures. Proc Natl Acad Sci U S A. 1995;92(16):7162-6.

45. Lipton SA, Nicotera P. Calcium, free radicals and excitotoxins in neuronal apoptosis. Cell Calcium. 1998;23(2-3):165-71.

46. Lipton SA. Paradigm shift in neuroprotection by NMDA receptor blockade: memantine and beyond. Nat Rev Drug Discov. 2006;5(2):160-70.

47. Hosenbocus S, Chahal R. Amantadine: a review of use in child and adolescent psychiatry. J Can Acad Child Adolesc Psychiatry. 2013;22(1):55-60.

48. Mohammadi MR, Mohammadzadeh S, Akhondzadeh S. Memantine versus Methylphenidate in Children and Adolescents with Attention Deficit Hyperactivity Disorder: A Double-Blind, Randomized Clinical Trial. Iran J Psychiatry. 2015;10(2):106-14.

49. Blanpied TA, Clarke RJ, Johnson JW. Amantadine inhibits NMDA receptors by accelerating channel closure during channel block. J Neurosci. 2005;25(13):3312-22.

50. Kornhuber J, Weller M, Schoppmeyer K, Riederer P. Amantadine and memantine are NMDA receptor antagonists with neuroprotective properties. J Neural Transm Suppl. 1994;43:91-104.

51. Johnson JW, Ascher P. Glycine potentiates the NMDA response in cultured mouse brain neurons. Nature. 1987;325(6104):529-31.

52. Madry C, Mesic I, Betz H, Laube B. The N-terminal domains of both NR1 and NR2 subunits determine allosteric Zn2+ inhibition and glycine affinity of N-methyl-D-aspartate receptors. Mol Pharmacol. 2007;72(6):1535-44.

53. Van Horn MR, Sild M, Ruthazer ES. D-serine as a gliotransmitter and its roles in brain development and disease. Front Cell Neurosci. 2013;7:39.

54. Kanahara N, Shimizu E, Ohgake S, Fujita Y, Kohno M, Hashimoto T, et al. Glycine and D: -serine, but not D: -cycloserine, attenuate prepulse inhibition deficits induced by NMDA receptor antagonist MK-801. Psychopharmacology (Berl). 2008;198(3):363-74.

55. Van Tol HH, Wu CM, Guan HC, Ohara K, Bunzow JR, Civelli O, et al. Multiple dopamine D4 receptor variants in the human population. Nature. 1992;358(6382):149-52.

56. Chang FM, Kidd JR, Livak KJ, Pakstis AJ, Kidd KK. The world-wide distribution of allele frequencies at the human dopamine D4 receptor locus. Hum Genet. 1996;98(1):91-101.

57. Trejo S, Toscano-Flores JJ, Matute E, Ramírez-Dueñas MeL. Hardy-Weinberg equilibrium analysis of the 48 bp VNTR in the III exon of the DRD4 gene in a sample of parents of ADHD cases. Appl Clin Genet. 2015;8:133-6.

58. Reiner I, Spangler G. Dopamine D4 receptor exon III polymorphism, adverse life events and personality traits in a nonclinical German adult sample. Neuropsychobiology. 2011;63(1):52-8.

59. Wang X, Zhong P, Gu Z, Yan Z. Regulation of NMDA receptors by dopamine D4 signaling in prefrontal cortex. J Neurosci. 2003;23(30):9852-61.

60. Qin L, Liu W, Ma K, Wei J, Zhong P, Cho K, et al. The ADHD-linked human dopamine D4 receptor variant D4.7 induces over-suppression of NMDA receptor function in prefrontal cortex. Neurobiol Dis. 2016;95:194-203.

61. Thomson AM, West DC, Lodge D. An N-methylaspartate receptor-mediated synapse in rat cerebral cortex: a site of action of ketamine? Nature. 1985;313(6002):479-81.

62. Fredriksson A, Archer T. Hyperactivity following postnatal NMDA antagonist treatment: reversal by D-amphetamine. Neurotox Res. 2003;5(7):549-64.

63. Fredriksson A, Archer T. Neurobehavioural deficits associated with apoptotic neurodegeneration and vulnerability for ADHD. Neurotox Res. 2004;6(6):435-56.

64. Bonhomme V, Vanhaudenhuyse A, Demertzi A, Bruno MA, Jaquet O, Bahri MA, et al. Resting-state Network-specific Breakdown of Functional Connectivity

during Ketamine Alteration of Consciousness in Volunteers. Anesthesiology. 2016;125(5):873-88.

65. Niesters M, Khalili-Mahani N, Martini C, Aarts L, van Gerven J, van Buchem MA, et al. Effect of subanesthetic ketamine on intrinsic functional brain connectivity: a placebo-controlled functional magnetic resonance imaging study in healthy male volunteers. Anesthesiology. 2012;117(4):868-77.

66. Hove MJ, Zeffiro TA, Biederman J, Li Z, Schmahmann J, Valera EM. Postural sway and regional cerebellar volume in adults with attention-deficit/hyperactivity disorder. Neuroimage Clin. 2015;8:422-8.

67. Kucyi A, Hove MJ, Biederman J, Van Dijk KR, Valera EM. Disrupted functional connectivity of cerebellar default network areas in attention-deficit/hyperactivity disorder. Hum Brain Mapp. 2015;36(9):3373-86.

68. Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, Hayes AJ, Carucci S, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2018;5(9):727-38.

69. Gainetdinov RR, Wetsel WC, Jones SR, Levin ED, Jaber M, Caron MG. Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity. Science. 1999;283(5400):397-401.

70. Gainetdinov RR, Mohn AR, Bohn LM, Caron MG. Glutamatergic modulation of hyperactivity in mice lacking the dopamine transporter. Proc Natl Acad Sci U S A. 2001;98(20):11047-54.

71. Masuo Y, Ishido M, Morita M, Oka S. Effects of neonatal 6-hydroxydopamine lesion on the gene expression profile in young adult rats. Neurosci Lett. 2002;335(2):124-8.

72. Miyamoto K, Nakanishi H, Moriguchi S, Fukuyama N, Eto K, Wakamiya J, et al. Involvement of enhanced sensitivity of N-methyl-D-aspartate receptors in vulnerability of developing cortical neurons to methylmercury neurotoxicity. Brain Res. 2001;901(1-2):252-8.

73. Volkow ND, Wang GJ, Fowler JS, Gatley SJ, Logan J, Ding YS, et al. Blockade of striatal dopamine transporters by intravenous methylphenidate is not sufficient to induce self-reports of "high". J Pharmacol Exp Ther. 1999;288(1):14-20.

74. Paladini CA, Fiorillo CD, Morikawa H, Williams JT. Amphetamine selectively blocks inhibitory glutamate transmission in dopamine neurons. Nat Neurosci. 2001;4(3):275-81.

75. Johnson LA, Furman CA, Zhang M, Guptaroy B, Gnegy ME. Rapid delivery of the dopamine transporter to the plasmalemmal membrane upon amphetamine stimulation. Neuropharmacology. 2005;49(6):750-8.

76. Cheng J, Xiong Z, Duffney LJ, Wei J, Liu A, Liu S, et al. Methylphenidate exerts dose-dependent effects on glutamate receptors and behaviors. Biol Psychiatry. 2014;76(12):953-62.

77. Bymaster FP, Katner JS, Nelson DL, Hemrick-Luecke SK, Threlkeld PG, Heiligenstein JH, et al. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. Neuropsychopharmacology. 2002;27(5):699-711.

78. Udvardi PT, Föhr KJ, Henes C, Liebau S, Dreyhaupt J, Boeckers TM, et al. Atomoxetine affects transcription/translation of the NMDA receptor and the norepinephrine transporter in the rat brain--an in vivo study. Drug Des Devel Ther. 2013;7:1433-46.

79. Ludolph AG, Udvardi PT, Schaz U, Henes C, Adolph O, Weigt HU, et al. Atomoxetine acts as an NMDA receptor blocker in clinically relevant concentrations. Br J Pharmacol. 2010;160(2):283-91.

80. Carrey N, MacMaster FP, Sparkes SJ, Khan SC, Kusumakar V. Glutamatergic changes with treatment in attention deficit hyperactivity disorder: a preliminary case series. J Child Adolesc Psychopharmacol. 2002;12(4):331-6.

81. Husarova V, Bittsansky M, Ondrejka I, Dobrota D. Prefrontal grey and white matter neurometabolite changes after atomoxetine and methylphenidate in children with attention deficit/hyperactivity disorder: a (1)H magnetic resonance spectroscopy study. Psychiatry Res. 2014;222(1-2):75-83.

82. Uhlén S, Xia Y, Chhajlani V, Felder CC, Wikberg JE. [3H]-MK 912 binding delineates two alpha 2-adrenoceptor subtypes in rat CNS one of which is identical with the cloned pA2d alpha 2-adrenoceptor. Br J Pharmacol. 1992;106(4):986-95.

83. Brennan AR, Arnsten AF. Neuronal mechanisms underlying attention deficit hyperactivity disorder: the influence of arousal on prefrontal cortical function. Ann N Y Acad Sci. 2008;1129:236-45.

84. Marrs W, Kuperman J, Avedian T, Roth RH, Jentsch JD. Alpha-2 adrenoceptor activation inhibits phencyclidine-induced deficits of spatial working memory in rats. Neuropsychopharmacology. 2005;30(8):1500-10.

85. Arnsten AF, Jin LE. Molecular influences on working memory circuits in dorsolateral prefrontal cortex. Prog Mol Biol Transl Sci. 2014;122:211-31.

86. Fredriksson I, Jayaram-Lindström N, Wirf M, Nylander E, Nyström E, Jardemark K, et al. Evaluation of guanfacine as a potential medication for alcohol use disorder in long-term drinking rats: behavioral and electrophysiological findings. Neuropsychopharmacology. 2015;40(5):1130-40.

87. Vitamin B6 (pyridoxine and pyridoxal 5'-phosphate) - monograph. Altern Med Rev. 2001;6(1):87-92.

88. Manor I, Ben-Hayun R, Aharon-Peretz J, Salomy D, Weizman A, Daniely Y, et al. A randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy, safety, and tolerability of extended-release metadoxine in adults with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2012;73(12):1517-23.

89. Manor I, Newcorn JH, Faraone SV, Adler LA. Efficacy of metadoxine extended release in patients with predominantly inattentive subtype attention-deficit/hyperactivity disorder. Postgrad Med. 2013;125(4):181-90.

90. Kim W, Tateno A, Arakawa R, Sakayori T, Ikeda Y, Suzuki H, et al. In vivo activity of modafinil on dopamine transporter measured with positron emission tomography and [^{18}F]FE-PE2I. Int J Neuropsychopharmacol. 2014;17(5):697-703.

91. Wisor J. Modafinil as a catecholaminergic agent: empirical evidence and unanswered questions. Front Neurol. 2013;4:139.

92. Tanganelli S, Ferraro L, Bianchi C, Fuxe K. 6-hydroxy-dopamine treatment counteracts the reduction of cortical GABA release produced by the vigilance promoting drug modafinil in the awake freely moving guinea-pig. Neurosci Lett. 1994;171(1-2):201-4.

93. Kumar R. Approved and investigational uses of modafinil : an evidence-based review. Drugs. 2008;68(13):1803-39.

94. Oka M, Itoh Y, Tatsumi S, Ma FH, Ukai Y, Yoshikuni Y, et al. A novel cognition enhancer NS-105 modulates adenylate cyclase activity through metabotropic glutamate receptors in primary neuronal culture. Naunyn Schmiedebergs Arch Pharmacol. 1997;356(2):189-96.

95. Oka M, Itoh Y, Shimidzu T, Ukai Y, Yoshikuni Y, Kimura K. Involvement of metabotropic glutamate receptors in Gi- and Gs-dependent modulation of adenylate cyclase activity induced by a novel cognition enhancer NS-105 in rat brain. Brain Res. 1997;754(1-2):121-30.

96. Hirouchi M, Oka M, Itoh Y, Ukai Y, Kimura K. Role of metabotropic glutamate receptor subclasses in modulation of adenylyl cyclase activity by a nootropic NS-105. Eur J Pharmacol. 2000;387(1):9-17.

97. Ogasawara T, Itoh Y, Tamura M, Mushiroi T, Ukai Y, Kise M, et al. Involvement of cholinergic and GABAergic systems in the reversal of memory disruption by NS-105, a cognition enhancer. Pharmacol Biochem Behav. 1999;64(1):41-52.

98. Shimidzu T, Itoh Y, Oka M, Ishima T, Ukai Y, Yoshikuni Y, et al. Effect of a novel cognition enhancer NS-105 on learned helplessness in rats: possible involvement of GABA(B) receptor up-regulation after repeated treatment. Eur J Pharmacol. 1997;338(3):225-32.

99. Elia J, Ungal G, Kao C, Ambrosini A, De Jesus-Rosario N, Larsen L, et al. Fasoracetam in adolescents with ADHD and glutamatergic gene network variants disrupting mGluR neurotransmitter signaling. Nat Commun. 2018;9(1):4.

100. Jin Z, Zang YF, Zeng YW, Zhang L, Wang YF. Striatal neuronal loss or dysfunction and choline rise in children with attention-deficit hyperactivity disorder: a 1H-magnetic resonance spectroscopy study. Neurosci Lett. 2001;315(1-2):45-8.

101. MacMaster FP, Carrey N, Sparkes S, Kusumakar V. Proton spectroscopy in

medication-free pediatric attention-deficit/hyperactivity disorder. Biol Psychiatry. 2003;53(2):184-7.

102. Courvoisie H, Hooper SR, Fine C, Kwock L, Castillo M. Neurometabolic functioning and neuropsychological correlates in children with ADHD-H: preliminary findings. J Neuropsychiatry Clin Neurosci. 2004;16(1):63-9.

103. Carrey NJ, MacMaster FP, Gaudet L, Schmidt MH. Striatal creatine and glutamate/glutamine in attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2007;17(1):11-7.

104. Naaijen J, Lythgoe DJ, Amiri H, Buitelaar JK, Glennon JC. Fronto-striatal glutamatergic compounds in compulsive and impulsive syndromes: a review of magnetic resonance spectroscopy studies. Neurosci Biobehav Rev. 2015;52:74-88.

105. Ende G, Cackowski S, Van Eijk J, Sack M, Demirakca T, Kleindienst N, et al. Impulsivity and Aggression in Female BPD and ADHD Patients: Association with ACC Glutamate and GABA Concentrations. Neuropsychopharmacology. 2016;41(2):410-8.

106. Perlov E, Philipsen A, Hesslinger B, Buechert M, Ahrendts J, Feige B, et al. Reduced cingulate glutamate/glutamine-to-creatine ratios in adult patients with attention deficit/hyperactivity disorder -- a magnet resonance spectroscopy study. J Psychiatr Res. 2007;41(11):934-41.

107. Edden RA, Crocetti D, Zhu H, Gilbert DL, Mostofsky SH. Reduced GABA concentration in attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 2012;69(7):750-3.

108. Ziemann U, Lönnecker S, Steinhoff BJ, Paulus W. The effect of lorazepam on the motor cortical excitability in man. Exp Brain Res. 1996;109(1):127-35.

109. Gilbert DL, Isaacs KM, Augusta M, Macneil LK, Mostofsky SH. Motor cortex inhibition: a marker of ADHD behavior and motor development in children. Neurology. 2011;76(7):615-21.

110. Boy F, Evans CJ, Edden RA, Singh KD, Husain M, Sumner P. Individual differences in subconscious motor control predicted by GABA concentration in SMA. Curr Biol. 2010;20(19):1779-85.

111. Nagamitsu S, Yamashita Y, Tanigawa H, Chiba H, Kaida H, Ishibashi M, et al. Upregulated GABA Inhibitory Function in ADHD Children with Child Behavior Checklist-Dysregulation Profile: 123I-Iomazenil SPECT Study. Front Psychiatry. 2015;6:84.

112. Carrey N, MacMaster FP, Fogel J, Sparkes S, Waschbusch D, Sullivan S, et al. Metabolite changes resulting from treatment in children with ADHD: a 1H-MRS study. Clin Neuropharmacol. 2003;26(4):218-21.

113. Marín-Padilla M. The mammalian neocortex new pyramidal neuron: a new conception. Front Neuroanat. 2014;7:51.

114. Herculano-Houzel S, Kaas JH, de Oliveira-Souza R. Corticalization of motor control in humans is a consequence of brain scaling in primate evolution. J Comp Neurol. 2016;524(3):448-55.

115. Azevedo FA, Carvalho LR, Grinberg LT, Farfel JM, Ferretti RE, Leite RE, et al. Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. J Comp Neurol. 2009;513(5):532-41.

116. DeFelipe J, Alonso-Nanclares L, Arellano JI. Microstructure of the neocortex: comparative aspects. J Neurocytol. 2002;31(3-5):299-316.

117. Fertuzinhos S, Krsnik Z, Kawasawa YI, Rasin MR, Kwan KY, Chen JG, et al. Selective depletion of molecularly defined cortical interneurons in human holoprosencephaly with severe striatal hypoplasia. Cereb Cortex. 2009;19(9):2196-207.

118. Hansen DV, Lui JH, Parker PR, Kriegstein AR. Neurogenic radial glia in the outer subventricular zone of human neocortex. Nature. 2010;464(7288):554-61.

119. Ma T, Wang C, Wang L, Zhou X, Tian M, Zhang Q, et al. Subcortical origins of human and monkey neocortical interneurons. Nat Neurosci. 2013;16(11):1588-97.

120. Verney C, Lebrand C, Gaspar P. Changing distribution of monoaminergic markers in the developing human cerebral cortex with special emphasis on the serotonin transporter. Anat Rec. 2002;267(2):87-93.

121. Daws LC, Gould GG. Ontogeny and regulation of the serotonin transporter: providing insights into human disorders. Pharmacol Ther. 2011;131(1):61-79.

122. Unis AS, Roberson MD, Robinette R, Ha J, Dorsa DM. Ontogeny of human brain dopamine receptors. I. Differential expression of [3H]-SCH23390 and [3H]-YM09151-2 specific binding. Brain Res Dev Brain Res. 1998;106(1-2):109-17.

123. Falk L, Nordberg A, Seiger A, Kjaeldgaard A, Hellström-Lindahl E. The alpha7 nicotinic receptors in human fetal brain and spinal cord. J Neurochem. 2002;80(3):457-65.

124. Letinic K, Zoncu R, Rakic P. Origin of GABAergic neurons in the human neocortex. Nature. 2002;417(6889):645-9.

125. Tao R, Li C, Newburn EN, Ye T, Lipska BK, Herman MM, et al. Transcript-specific associations of SLC12A5 (KCC2) in human prefrontal cortex with development, schizophrenia, and affective disorders. J Neurosci. 2012;32(15):5216-22.

126. Elston GN, Benavides-Piccione R, Elston A, Manger PR, Defelipe J. Pyramidal cells in prefrontal cortex of primates: marked differences in neuronal structure among species. Front Neuroanat. 2011;5:2.

127. Kew JN, Kemp JA. Ionotropic and metabotropic glutamate receptor structure and pharmacology. Psychopharmacology (Berl). 2005;179(1):4-29.

128. Pleasure D. Diagnostic and pathogenic significance of glutamate receptor autoantibodies. Arch Neurol. 2008;65(5):589-92.

129. Conti F, Weinberg RJ. Shaping excitation at glutamatergic synapses. Trends Neurosci. 1999;22(10):451-8.

130. Bergles DE, Roberts JD, Somogyi P, Jahr CE. Glutamatergic synapses on oligodendrocyte precursor cells in the hippocampus. Nature. 2000;405(6783):187-91.

131. Shelton MK, McCarthy KD. Mature hippocampal astrocytes exhibit functional metabotropic and ionotropic glutamate receptors in situ. Glia. 1999;26(1):1-11.

132. Steinhäuser C, Gallo V. News on glutamate receptors in glial cells. Trends Neurosci. 1996;19(8):339-45.

133. Vernadakis A. Glia-neuron intercommunications and synaptic plasticity. Prog Neurobiol. 1996;49(3):185-214.

134. Ritter LM, Unis AS, Meador-Woodruff JH. Ontogeny of ionotropic glutamate receptor expression in human fetal brain. Brain Res Dev Brain Res. 2001;127(2):123-33.

135. Lee H, Choi BH. Density and distribution of excitatory amino acid receptors in the developing human fetal brain: a quantitative autoradiographic study. Exp Neurol. 1992;118(3):284-90.

136. Jantzie LL, Talos DM, Selip DB, An L, Jackson MC, Folkerth RD, et al. Developmental regulation of group I metabotropic glutamate receptors in the premature brain and their protective role in a rodent model of periventricular leukomalacia. Neuron Glia Biol. 2010;6(4):277-88.

137. Gressens P. Mechanisms and disturbances of neuronal migration. Pediatr Res. 2000;48(6):725-30.

138. Letinic K, Rakic P. Telencephalic origin of human thalamic GABAergic neurons. Nat Neurosci. 2001;4(9):931-6.

139. Molliver ME, Kostović I, van der Loos H. The development of synapses in cerebral cortex of the human fetus. Brain Res. 1973;50(2):403-7.

140. Zecevic N. Synaptogenesis in layer I of the human cerebral cortex in the first half of gestation. Cereb Cortex. 1998;8(3):245-52.

141. Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol. 1997;387(2):167-78.

142. Ben-Ari Y. The GABA excitatory/inhibitory developmental sequence: a personal journey. Neuroscience. 2014;279:187-219.

143. Bonifazi P, Goldin M, Picardo MA, Jorquera I, Cattani A, Bianconi G, et al. GABAergic hub neurons orchestrate synchrony in developing hippocampal networks. Science. 2009;326(5958):1419-24.

144. Picardo MA, Guigue P, Bonifazi P, Batista-Brito R, Allene C, Ribas A, et al. Pioneer GABA cells comprise a subpopulation of hub neurons in the developing hippocampus. Neuron. 2011;71(4):695-709.

145. de Graaf-Peters VB, Hadders-Algra M. Ontogeny of the human central nervous system: what is happening when? Early Hum Dev. 2006;82(4):257-66.

146. Allen NJ, Eroglu C. Cell Biology of Astrocyte-Synapse Interactions. Neuron. 2017;96(3):697-708.

147. Reemst K, Noctor SC, Lucassen PJ, Hol EM. The Indispensable Roles of Microglia and Astrocytes during Brain Development. Front Hum Neurosci. 2016;10:566.

148. Khakh BS, McCarthy KD. Astrocyte calcium signaling: from observations to functions and the challenges therein. Cold Spring Harb Perspect Biol. 2015;7(4):a020404.

149. Allen NJ. Astrocyte regulation of synaptic behavior. Annu Rev Cell Dev Biol. 2014;30:439-63.

150. Araque A, Carmignoto G, Haydon PG, Oliet SH, Robitaille R, Volterra A. Gliotransmitters travel in time and space. Neuron. 2014;81(4):728-39.

151. Back SA, Luo NL, Borenstein NS, Levine JM, Volpe JJ, Kinney HC. Late oligodendrocyte progenitors coincide with the developmental window of vulnerability for human perinatal white matter injury. J Neurosci. 2001;21(4):1302-12.

152. Jakovcevski I, Zecevic N. Sequence of oligodendrocyte development in the human fetal telencephalon. Glia. 2005;49(4):480-91.

153. Jakovcevski I, Filipovic R, Mo Z, Rakic S, Zecevic N. Oligodendrocyte development and the onset of myelination in the human fetal brain. Front Neuroanat. 2009;3:5.

154. Liston C, Malter Cohen M, Teslovich T, Levenson D, Casey BJ. Atypical prefrontal connectivity in attention-deficit/hyperactivity disorder: pathway to disease or pathological end point? Biol Psychiatry. 2011;69(12):1168-77.

155. van Ewijk H, Heslenfeld DJ, Zwiers MP, Buitelaar JK, Oosterlaan J. Diffusion tensor imaging in attention deficit/hyperactivity disorder: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2012;36(4):1093-106.

156. Almeida RG, Lyons DA. On Myelinated Axon Plasticity and Neuronal Circuit Formation and Function. J Neurosci. 2017;37(42):10023-34.

157. Falk S, Götz M. Glial control of neurogenesis. Curr Opin Neurobiol. 2017;47:188-95.

158. Ginhoux F, Prinz M. Origin of microglia: current concepts and past controversies. Cold Spring Harb Perspect Biol. 2015;7(8):a020537.

159. Kierdorf K, Prinz M. Microglia in steady state. J Clin Invest. 2017;127(9):3201-9.

160. Li Q, Barres BA. Microglia and macrophages in brain homeostasis and disease. Nat Rev Immunol. 2018;18(4):225-42.

161. Salter MW, Stevens B. Microglia emerge as central players in brain disease. Nat Med. 2017;23(9):1018-27.

162. Wolf SA, Boddeke HW, Kettenmann H. Microglia in Physiology and Disease. Annu Rev Physiol. 2017;79:619-43.

163. Gumusoglu SB, Stevens HE. Maternal Inflammation and Neurodevelopmental Programming: A Review of Preclinical Outcomes and Implications for Translational Psychiatry. Biol Psychiatry. 2019;85(2):107-21.

164. Semple BD, Blomgren K, Gimlin K, Ferriero DM, Noble-Haeusslein LJ. Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. Prog Neurobiol. 2013;106-107:1-16.

165. Tebbenkamp AT, Willsey AJ, State MW, Sestan N. The developmental transcriptome of the human brain: implications for neurodevelopmental disorders. Curr Opin Neurol. 2014;27(2):149-56.

166. Lou HC. Etiology and pathogenesis of attention-deficit hyperactivity disorder (ADHD): significance of prematurity and perinatal hypoxic-haemodynamic encephalopathy. Acta Paediatr. 1996;85(11):1266-71.

167. Choi DW. Glutamate receptors and the induction of excitotoxic neuronal death. Prog Brain Res. 1994;100:47-51.

168. Bakiri Y, Burzomato V, Frugier G, Hamilton NB, Káradóttir R, Attwell D. Glutamatergic signaling in the brain's white matter. Neuroscience. 2009;158(1):266-74.

169. Holopainen IE, Laurén HB. Glutamate signaling in the pathophysiology and therapy of prenatal insults. Pharmacol Biochem Behav. 2012;100(4):825-34.

170. Matute C. Glutamate and ATP signalling in white matter pathology. J Anat. 2011;219(1):53-64.

171. Gupta K, Hardingham GE, Chandran S. NMDA receptor-dependent glutamate excitotoxicity in human embryonic stem cell-derived neurons. Neurosci Lett. 2013;543:95-100.

172. Ikonomidou C, Bosch F, Miksa M, Bittigau P, Vöckler J, Dikranian K, et al. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science. 1999;283(5398):70-4.

173. Reynolds JD, Brien JF. Ethanol neurobehavioural teratogenesis and the role of L-glutamate in the fetal hippocampus. Can J Physiol Pharmacol. 1995;73(9):1209-23.

174. Meyer LS, Kotch LE, Riley EP. Alterations in gait following ethanol exposure during the brain growth spurt in rats. Alcohol Clin Exp Res. 1990;14(1):23-7.

175. Lovinger DM, White G, Weight FF. Ethanol inhibits NMDA-activated ion current in hippocampal neurons. Science. 1989;243(4899):1721-4.

176. White PF, Way WL, Trevor AJ. Ketamine--its pharmacology and therapeutic uses. Anesthesiology. 1982;56(2):119-36.

177. Jevtović-Todorović V, Todorović SM, Mennerick S, Powell S, Dikranian K, Benshoff N, et al. Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med. 1998;4(4):460-3.

178. Deng W, Wang H, Rosenberg PA, Volpe JJ, Jensen FE. Role of metabotropic glutamate receptors in oligodendrocyte excitotoxicity and oxidative stress. Proc Natl Acad Sci U S A. 2004;101(20):7751-6.

179. Thion MS, Ginhoux F, Garel S. Microglia and early brain development: An intimate journey. Science. 2018;362(6411):185-9.

180. Smith SE, Li J, Garbett K, Mirnics K, Patterson PH. Maternal immune activation alters fetal brain development through interleukin-6. J Neurosci. 2007;27(40):10695-702.

181. Squarzoni P, Oller G, Hoeffel G, Pont-Lezica L, Rostaing P, Low D, et al. Microglia modulate wiring of the embryonic forebrain. Cell Rep. 2014;8(5):1271-9.

182. Hanamsagar R, Alter MD, Block CS, Sullivan H, Bolton JL, Bilbo SD. Generation of a microglial developmental index in mice and in humans reveals a sex difference in maturation and immune reactivity. Glia. 2017;65(9):1504-20.

183. Rudolph MD, Graham AM, Feczko E, Miranda-Dominguez O, Rasmussen JM, Nardos R, et al. Maternal IL-6 during pregnancy can be estimated from newborn brain connectivity and predicts future working memory in offspring. Nat Neurosci. 2018;21(5):765-72.

184. Estes ML, McAllister AK. Maternal immune activation: Implications for neuropsychiatric disorders. Science. 2016;353(6301):772-7.

185. Lydholm CN, Köhler-Forsberg O, Nordentoft M, Yolken RH, Mortensen PB, Petersen L, et al. Parental Infections Before, During, and After Pregnancy as Risk Factors for Mental Disorders in Childhood and Adolescence: A Nationwide Danish Study. Biol Psychiatry. 2019;85(4):317-25.

186. Susser E, Bresnahan M, Lipkin WI. Interpreting New Evidence on Prenatal Infections and Mental Disorders. Biol Psychiatry. 2019;85(4):285-6.

187. van Gelder MM, van Rooij IA, Miller RK, Zielhuis GA, de Jong-van den Berg LT, Roeleveld N. Teratogenic mechanisms of medical drugs. Hum Reprod Update. 2010;16(4):378-94.

188. Berghuis P, Rajnicek AM, Morozov YM, Ross RA, Mulder J, Urbán GM, et al. Hardwiring the brain: endocannabinoids shape neuronal connectivity. Science. 2007;316(5828):1212-6.

189. Trazzi S, Steger M, Mitrugno VM, Bartesaghi R, Ciani E. CB1 cannabinoid receptors increase neuronal precursor proliferation through AKT/glycogen synthase kinase-3beta/beta-catenin signaling. J Biol Chem. 2010;285(13):10098-109.

190. Díaz-Alonso J, Aguado T, Wu CS, Palazuelos J, Hofmann C, Garcez P, et al. The CB(1) cannabinoid receptor drives corticospinal motor neuron differentiation through the Ctip2/Satb2 transcriptional regulation axis. J Neurosci. 2012;32(47):16651-65.

191. Mereu G, Fà M, Ferraro L, Cagiano R, Antonelli T, Tattoli M, et al. Prenatal exposure to a cannabinoid agonist produces memory deficits linked to dysfunction in hippocampal long-term potentiation and glutamate release. Proc Natl Acad Sci U S A. 2003;100(8):4915-20.

192. Antonelli T, Tomasini MC, Tattoli M, Cassano T, Tanganelli S, Finetti S, et al. Prenatal exposure to the CB1 receptor agonist WIN 55,212-2 causes learning disruption associated with impaired cortical NMDA receptor function and emotional reactivity changes in rat offspring. Cereb Cortex. 2005;15(12):2013-20.

193. Saez TM, Aronne MP, Caltana L, Brusco AH. Prenatal exposure to the CB1 and CB2 cannabinoid receptor agonist WIN 55,212-2 alters migration of early-born glutamatergic neurons and GABAergic interneurons in the rat cerebral cortex. J Neurochem. 2014;129(4):637-48.

194. Dark C, Homman-Ludiye J, Bryson-Richardson RJ. The role of ADHD associated genes in neurodevelopment. Dev Biol. 2018;438(2):69-83.

195. Matsugami TR, Tanemura K, Mieda M, Nakatomi R, Yamada K, Kondo T, et al. From the Cover: Indispensability of the glutamate transporters GLAST and GLT1 to brain development. Proc Natl Acad Sci U S A. 2006;103(32):12161-6.

196. Aida T, Ito Y, Takahashi YK, Tanaka K. Overstimulation of NMDA receptors impairs early brain development in vivo. PLoS One. 2012;7(5):e36853.

197. Ascoli GA, Alonso-Nanclares L, Anderson SA, Barrionuevo G, Benavides-Piccione R, Burkhalter A, et al. Petilla terminology: nomenclature of features of GABAergic interneurons of the cerebral cortex. Nat Rev Neurosci. 2008;9(7):557-68.

198. Gupta K, Patani R, Baxter P, Serio A, Story D, Tsujita T, et al. Human embryonic stem cell derived astrocytes mediate non-cell-autonomous neuroprotection through endogenous and drug-induced mechanisms. Cell Death Differ. 2012;19(5):779-87.

199. Zeisel A, Muñoz-Manchado AB, Codeluppi S, Lönnerberg P, La Manno G, Juréus A, et al. Brain structure. Cell types in the mouse cortex and hippocampus revealed by single-cell RNA-seq. Science. 2015;347(6226):1138-42.

200. Tasic B, Menon V, Nguyen TN, Kim TK, Jarsky T, Yao Z, et al. Adult mouse cortical cell taxonomy revealed by single cell transcriptomics. Nat Neurosci. 2016;19(2):335-46.

201. Markram H, Muller E, Ramaswamy S, Reimann MW, Abdellah M, Sanchez CA, et al. Reconstruction and Simulation of Neocortical Microcircuitry. Cell. 2015;163(2):456-92.

202. Jiang X, Shen S, Cadwell CR, Berens P, Sinz F, Ecker AS, et al. Principles of connectivity among morphologically defined cell types in adult neocortex. Science. 2015;350(6264):aac9462.

203. Lake BB, Ai R, Kaeser GE, Salathia NS, Yung YC, Liu R, et al. Neuronal subtypes and diversity revealed by single-nucleus RNA sequencing of the human brain. Science. 2016;352(6293):1586-90.

204. Favuzzi E, Deogracias R, Marques-Smith A, Maeso P, Jezequel J, Exposito-Alonso D, et al. Distinct molecular programs regulate synapse specificity in cortical inhibitory circuits. Science. 2019;363(6425):413-7.

205. Moffitt JR, Bambah-Mukku D, Eichhorn SW, Vaughn E, Shekhar K, Perez JD, et al. Molecular, spatial, and functional single-cell profiling of the hypothalamic preoptic region. Science. 2018;362(6416).

206. Boldog E, Bakken TE, Hodge RD, Novotny M, Aevermann BD, Baka J, et al. Transcriptomic and morphophysiological evidence for a specialized human cortical GABAergic cell type. Nat Neurosci. 2018;21(9):1185-95.

207. Amiri A, Coppola G, Scuderi S, Wu F, Roychowdhury T, Liu F, et al. Transcriptome and epigenome landscape of human cortical development modeled in organoids. Science. 2018;362(6420).