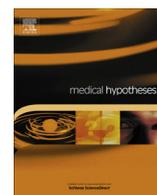




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Methylphenidate and the juvenile brain: Enhancement of attention at the expense of cortical plasticity?



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ABSTRACT

Methylphenidate (Ritalin) is the most commonly prescribed psychoactive drug for juveniles and adolescents. Used to treat attention-deficit/hyperactivity disorder (ADHD) and for cognitive enhancement in healthy individuals, it has been regarded as a relatively safe medication for the past several decades. However, a thorough review of the literature reveals that the age-dependent activities of the drug, as well as potential developmental effects, are largely ignored. In addition, the diagnosis of ADHD is subjective, leaving open the possibility of misdiagnosis and excessive prescription of the drug. Recent studies have suggested that early life exposure of healthy rodent models to methylphenidate resulted in altered sleep/wake cycle, heightened stress reactivity, and, in fact, a dosage previously thought of as therapeutic depressed neuronal function in juvenile rats. Furthermore, juvenile rats exposed to low-dose methylphenidate displayed alterations in neural markers of plasticity, indicating that the drug might alter the basic properties of prefrontal cortical circuits. In this review of the current literature, we propose that juvenile exposure to methylphenidate may cause abnormal prefrontal function and impaired plasticity in the healthy brain, strengthening the case for developing a more thorough understanding of methylphenidate's actions on the developing, juvenile brain, as well as better diagnostic measures for ADHD.

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Attention deficit/hyperactivity disorder (ADHD) is one of the most commonly diagnosed pediatric behavioral disorders, with current estimates ranging from 3% to 5% of the population globally [1,2]. The number of children diagnosed with ADHD skyrocketed 24% between 2001 and 2010, according to a recent study published in *JAMA Pediatrics* [3]. Symptoms of ADHD can persist well into adulthood, and include inattentiveness, hyperactivity and impulsivity, often occurring along with other behavioral disorders or mood disorders [4,5]. If left untreated, the effects can be devastating, preventing the affected individual from functioning successfully in a classroom or job setting, and negatively impacting social relationships [6,7].

While the exact mechanisms of the disease have not been discovered, it is thought that ADHD symptoms arise from hypoactivity of the prefrontal cortex, which in turn arises from a lack of innervation from the neurotransmitter systems of dopamine and norepinephrine [8]. They are of particular importance to the proper function of the prefrontal cortex. This portion of the brain sits in the frontal-most area of the cortex, above the eyes and extending back to the temples. The prefrontal cortex is the brain's "executive control center," integrating sensory and motor information, direct-

ing attention, and planning behaviors [9–12] (Fig. 1). Hypoactivity in this region results in locomotor hyperactivity, impulsivity, inability to properly direct attention, and often manifests as poor performance in school or at work [8].

Methylphenidate (Ritalin®; MPH) is currently the most commonly prescribed medication for the treatment of ADHD [13]. Methylphenidate is a psychostimulant, related to amphetamine, cocaine, and caffeine, and exerts its effects by blocking the transporters that reuptake dopamine and norepinephrine into the presynaptic neuron following their release; thus, it increases the levels or prolongs the availability of these neurotransmitters in the synapses to exert effects on postsynaptic neurons [14–16]. In optimal amounts, dopamine acts via the D1-like receptors, and norepinephrine via the α 2A receptors to increase signal-to-noise ratio in the prefrontal cortex; thus enhancing the flow of information and neuronal communication [9,17]. Excessive levels of dopamine and norepinephrine begin to activate dopamine D2-class receptors and noradrenergic α 2 and β receptors, leading to weakening of the signal-to-noise ratio, and activation of neurons that may not be involved in the current task [9]. However, a recent study suggested that prefrontal cortex-dependent processes display differential sensitivity to the cognition-enhancing actions of psychostimulants that are linked to the differential involvement of α 1- versus α 2-receptors in these processes [18].

A large proportion of the literature on mechanisms of action of methylphenidate and dose-response curves comes from studies

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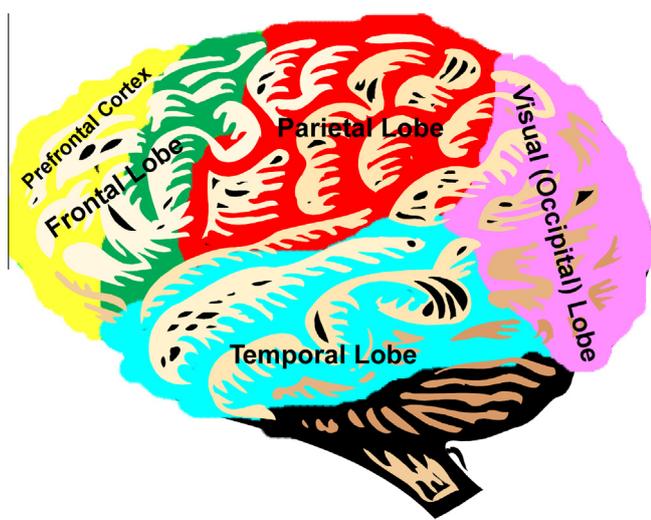


Fig. 1. The prefrontal cortex (highlighted in yellow) is the brain's executive control center, involved in regulating working memory, attention, thinking, decision-making, judgment, behavioral control/inhibition, and emotion and motivation. The prefrontal cortex lies in the front-most portion of the frontal lobe (yellow and green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

performed on normal human and animal subjects [18–22]. At first thought, this may seem like a glaring weakness – how could studying the actions of a drug on a normal population represent its effects on a diseased subset? It is important to note that reduced hyperactivity and impulsivity in stimulant-treated ADHD patients were not “paradoxical” effects, but in fact also occurred in healthy individuals given the same doses [23,24]. The ability of low-dose stimulants to increase sustained attention, improve response inhibition and decrease locomotor activity is not unique to patients with ADHD. All of these actions are observed in non-ADHD humans and normal animals [25–27]. Additionally, low-dose MPH exerts similar actions on PFC neuronal activity (assessed by functional MRI) in a go/no-go task in both ADHD patients and normal control subjects [26]. Thus, the therapeutic actions of stimulants used to treat ADHD are not unique to ADHD patients nor do they necessarily reflect pathology within catecholaminergic systems in ADHD. Similar evidence exists to validate investigations of MPH actions in normal, experimental animals. More recent MPH studies in both humans and rats have found that low doses of MPH that correspond to those given to ADHD patients in the clinic appear to enhance prefrontal-dependent functions and cognition in much the same way in healthy humans and rats as they do in ADHD patients and disease model rat strains [1,25,28–34]. Therefore, study of the behavioral and physiological actions of clinically and behaviorally relevant doses of MPH in normal animals provides an opportunity to explore the role of catecholamine transmitters in prefrontal cortical function and attentional processes as they relate to the dynamic operation of brain circuits under normal and abnormal (e.g. ADHD) conditions.

This fact, along with the lack of reliable animal models of ADHD, led to the acceptance of stimulant study in healthy human subjects and in normal animals. Studying methylphenidate's effects in healthy individuals can provide valuable insights into the drug's mechanisms of action, as well as potentially highlight differences between ADHD-diseased and healthy brains. Higher doses (doses greater than those given to treat ADHD) increase locomotor activity and impair attention and performance on prefrontal cortex-dependent cognitive tasks; however, lower doses (those equivalent to the range given to ADHD patients) improve cognitive perfor-

mance and reduce locomotor activity in healthy individuals [18,19,25,35]. Likewise, lower doses of methylphenidate (0.25–1 mg/kg, intraperitoneal, i.p.) in normal adult rats resulted in increased performance on attention tasks along with no effect on locomotor activity, while higher doses impaired performance and induced hyperactivity; doses beyond 10 mg/kg resulted in “stereotypies” (repetitive, fine motor movements similar to the tics seen in disorders like Tourette's syndrome) [25,36,37]. Why might a medication that is reportedly a stimulant result in increased focus and attention while reducing locomotor hyperactivity? The answer lies in the regulation of dopamine and norepinephrine. Low, cognition enhancing doses of MPH have been shown to cause increases in these neurotransmitters selectively in prefrontal cortex, resulting in a heightening of executive functions without altering locomotion or physical activity levels (as would be seen if striatum were activated by the drug) [38]. However, higher doses of MPH (above 5–10 mg/kg) have been shown to indiscriminately activate other cortical regions, resulting in an overshoot of dopamine and norepinephrine, depressing neuronal function in prefrontal cortex and inducing hyperactivity and stereotypies [39,40]. The inverted U-curve of dopamine/norepinephrine actions on prefrontal function has been well illustrated [18,21,41–44]. Specifically, low, cognition-enhancing doses of MPH purportedly induce only slight increase of these neurotransmitters, optimizing function and placing the levels at the “peak” of that curve. However, when dosages of MPH are further increased, the levels surpass the peak and fall along the right hand of the curve, where over-excitation and stimulation of cAMP pathways begin to cause hyperactivity, impulsivity, over-stimulation and distractibility. Levels of dopamine and norepinephrine in a normal, healthy brain are not static; they may fall at the optimal peak for that individual, slightly less, or slightly more than optimal. There is currently no method for determining the optimal levels of these neurotransmitters in each individual; thus, predicting how psychostimulants will act is mainly guess-work. It is also possible that, although many studies found no overt cognitive differences between the effects of low-dose MPH on normal individuals and ADHD patients, molecular or cellular differences that cannot be detected in humans with our current technology might exist. Thus, one must examine the research on MPH as a cognitive enhancer and studies using normal individuals with caution and a critical mind.

Whatever the actual neuronal consequences of its usage may be, MPH is a hot-topic in research today, and is increasingly studied and accepted as a cognitive enhancer. MPH is frequently sold on the “black market” at schools and universities, and is used/abused more and more by graduate and medical students, military personnel, doctors and lawyers – any high-stress position where cognitive ability is highly valued [45,46]. This frequent off-label usage stresses the need for a deeper understanding of its actions and effects on the brain.

It is not only the issue of healthy vs. ADHD-diseased brains that clouds our understanding of MPH's actions – the vast majority of animal research has been conducted on mature rats, whereas the drug is most commonly given to children. These studies conducted in adult animals have provided great insights into the actions and potential side effects of MPH. However, because MPH is mostly used to treat children with ADHD, abused by teenagers as learning drugs, and the prefrontal cortex is still developing during this time, it is particularly important to investigate the drug's effects on juvenile and adolescent brain systems. It is not hard to imagine that the adult brain may react differently to MPH treatment than would a juvenile, still developing brain [6]. The prefrontal cortex does not finish development until young adulthood; in humans this falls around the end of the second decade or early third decade of life [47–50]. This late prefrontal cortical development is of particular relevance to the development of ADHD [51]; levels of

norepinephrine and dopamine surge and wane during maturation of the prefrontal cortex, and disruptions to the developmental flow may be responsible for some of the symptoms [52]. This development and remodeling of the neurotransmitter systems implicated in ADHD reveals a period of vulnerability during which insults to the system might change the developmental course and cause lasting alterations in the neurotransmitter levels.

In fact, a small, recently emerging body of research has begun to demonstrate the differential actions of MPH on juvenile versus adult animals. These studies have found that juvenile treatment with fairly low doses of methylphenidate resulted in disruption of the sleep/wake cycle and heightened anxiety responses even into adulthood [53,54]. There have also been conflicting studies examining sensitization and vulnerability to drug abuse in children or adolescent rodents exposed to methylphenidate early in life, although more recent studies seem to agree that early life treatment with therapeutic doses protects against drug abuse and resolves complications of ADHD [55].

Despite the increasing usage of young rats in MPH research, no attempt has been made to determine if there is a difference in the rate of metabolism of MPH between juvenile rats and adult rats – given the higher basal metabolic and growth rates of juvenile rats, it would stand to reason that differences in the speed of metabolism and breakdown of pharmaceuticals such as MPH would be evident. While no study has yet examined the specific metabolism of MPH in juvenile rats, it should be noted that adolescent rats (PD40–45) that received 10 mg/kg i.p. of MPH displayed increased brain glucose metabolism across most brain regions [56]. This dosage is far beyond the clinical range (0.5–2 mg/kg i.p.), but it does suggest that MPH increases brain metabolic rate in juvenile rats. Therefore, if metabolic rates differ between juvenile and adult rats, the dose-response curve and therapeutic range might differ as well. Given the inconsistencies of current juvenile rat MPH studies, and the wide range of doses used in these studies, it is imperative to determine a proper therapeutic range for juvenile rats following both injected and orally-administered MPH, as well as to determine if early life exposure has the potential to cause lasting alterations in basic function of the prefrontal cortex.

One important unique property of the prefrontal cortex is its high level of plasticity, allowing for executive functions like working memory and active decision-making; this plasticity may be a product of the slow maturation of this region [51,57,58]. Plasticity in the brain refers to the ability of the circuits to weaken or strengthen neuronal pathways based on the environment and the individual's experiences; it is the brain's flexibility. It is plasticity that allows us to learn, remember, and also to forget past lessons that are no longer applicable in the present. When we are young, all areas of the brain are highly plastic, allowing the circuitry involved in motor movements and sensory input to form; however, once adulthood is reached, the cortex becomes more rigid. The prefrontal cortex, however, retains that high level of plasticity throughout life, especially during the juvenile and adolescent period, and it is thought that this is necessary for working memory, behavioral inhibition, judgment, and decision-making [51]. The plasticity, at least in part, is thought to be due to a unique composition of NMDA receptors, a major receptor type involved in excitatory glutamatergic synaptic transmission [59–62]. NMDA receptors all contain two NR1 subunits, and also contain either NR2A or NR2B; NR2B conveys slower kinetics to the channel, allowing it to remain partially open during multiple stimulations [61]. This results in summation of responses and the continuation of neural activity briefly after input has stopped [62]. Without this unique feature, we would not be able to hold information in our minds during attention/working memory tasks, like remembering a phone number long enough to write it down, or walking into another room to fetch something [63]. It is unclear whether treat-

ment with MPH during adolescence will alter the developmental course of the prefrontal cortex. However, it is apparent that developmental age does play a critical role in determining the effects of drug administration on prefrontal neurons. Based on this review of the current literature, we hypothesize that MPH within the reportedly therapeutic range will induce distinct biochemical and physiological changes in the developing brain. Specifically, treatment with MPH will result in significant changes in neuronal excitability, synaptic transmission and plasticity in the prefrontal neurons in juvenile rats. We have designed the following experiments to test this intriguing hypothesis.

First, as we recently reported, we found that treatment with MPH resulted in significant reduction in both excitability and synaptic transmission in the juvenile rat prefrontal cortical neurons [64] (Fig. 2A and C). This reduction in excitability may seem counterintuitive, as the drug has previously been found to increase cortical excitability at low doses; it is this increase in neuronal activity that is thought of as a therapeutic effect [38]. The reason for these discrepancies is unknown, but it would appear that juvenile rat prefrontal neurons are supersensitive to MPH and that the observed effects are age-dependent. The juvenile results were opposite to those seen in adult rats, in which prefrontal neurons are excited by low-dose stimulant treatment [35,65] or by systemic administration of 2 mg/kg MPH [66]. Taken together, these results argue for an age-dependent action of MPH on prefrontal neurons. However, how this cellular depression occurs, and what effects it may have on circuitry level function remain unclear and further study on this issue is warranted.

In order to understand the potential effects of MPH on cortical plasticity in the juvenile brain, one must look beyond the dopamine/norepinephrine systems, to the glutamate system, which is mostly involved in regulating plasticity via AMPA and NMDA receptors. The dopaminergic and glutamatergic systems are intricately interlinked via signaling pathways as well as physical interactions [67]. NMDARs control acute plasticity by regulating trafficking of AMPARs to the postsynaptic sites – AMPARs are associated with excitability of neurons and parameters such as spike timing and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. During development, NR2B-containing subunits are replaced by NR2A-containing ones in the NMDA receptors, raising the threshold for LTP but lowering for LTD, making learning more selective [68]. A high percentage of NR2B-containing NMDA receptors lowers the threshold for LTP, and therefore increases the rate of learning and long-term memory formation, while a high percentage of NR2A-containing receptors lowers the threshold for LTD, increasing extinction and decreasing formation of long-term memories of the current situation [68]. Since NR2B levels should remain high in prefrontal cortex throughout life [62], any substance that decreases the levels of NR2B would likely cause a dampening of this region's innate plasticity. A recent study by our lab indicated that excessive levels of dopamine indiscriminately activate the D2-like receptors, which result in a reduction in NMDAR trafficking via disruption of cAMP-independent glycogen synthase kinase 3 beta (GSK-3 β) signaling pathway [69]. Furthermore, amphetamine has been shown to cause selective internalization and degradation of NR2B subunits, with no effect on NR2A levels [70]. We also found that when juvenile rats were treated with a single (1 mg/kg, i.p.) dose of methylphenidate, the levels of NR2B protein, as well as NR1, in the prefrontal cortex was markedly reduced, while NR2A levels did not change [64]. The behavioral and functional consequences of such a specific decrease in NR1 and NR2B levels are striking and potentially devastating to proper prefrontal cortical function. The prefrontal cortex is unique among cortical regions in that it does not experience a significant alteration in the NR2A/B ratio during development [62]. Thus, selectively decreasing the levels of NR2B-containing NMDA

receptors in the prefrontal cortex might remove this region's unique plasticity, rendering the prefrontal cortex similar to other cortical regions and potentially altering or impairing executive function. Indeed, following juvenile rat treatment with a single dose of 1 mg/kg MPH, our lab saw a significant decrease in NMDA receptor-mediated excitatory postsynaptic currents in response to 20-Hz train stimulation (Fig. 2D and E). Furthermore, we also observed a shifting of long-term potentiation in the MPH-treated juvenile rat brain towards potentiation, with long-term potentiation significantly enhanced, while long-term depression was reduced [71]. These results indicate that treatment of the juvenile brain with clinically-relevant, low doses of MPH may alter plasticity of the prefrontal cortex. How might these changes manifest behaviorally? It is as of yet unclear; however, one hypothesis is that MPH may affect the integration of incoming signals and thus impair memory function in the juvenile brain. But the question is how? The prefrontal cortex's uniquely high levels of NR2B

throughout life impart the ability of the neurons to summate responses to incoming stimuli, resulting in the short-term potentiation of neural activity necessary for working memory; thus, decreasing the levels of NR2B in prefrontal cortex leads to reduction in the summation, which should impair working memory [62,63,71]. However, long-term potentiation is enhanced upon treatment with MPH [71]. Long-term potentiation was found to be enhanced following juvenile treatment with MPH. The exact roles of NR2A versus NR2B receptor subunits in long-term potentiation regulation in the prefrontal cortex are not well understood, but it is currently believed that the direction of plasticity in prefrontal cortex (potentiation or depression) is dependent on the ratio of NR2A/NR2B, rather than exact levels of each subunit [59,60,72–74]. Thus, reducing NR2B levels without altering NR2A levels, as was seen following juvenile MPH treatment, was enough to alter the direction of long-term plasticity in the prefrontal cortex [71]. The behavioral ramifications of altering long-term

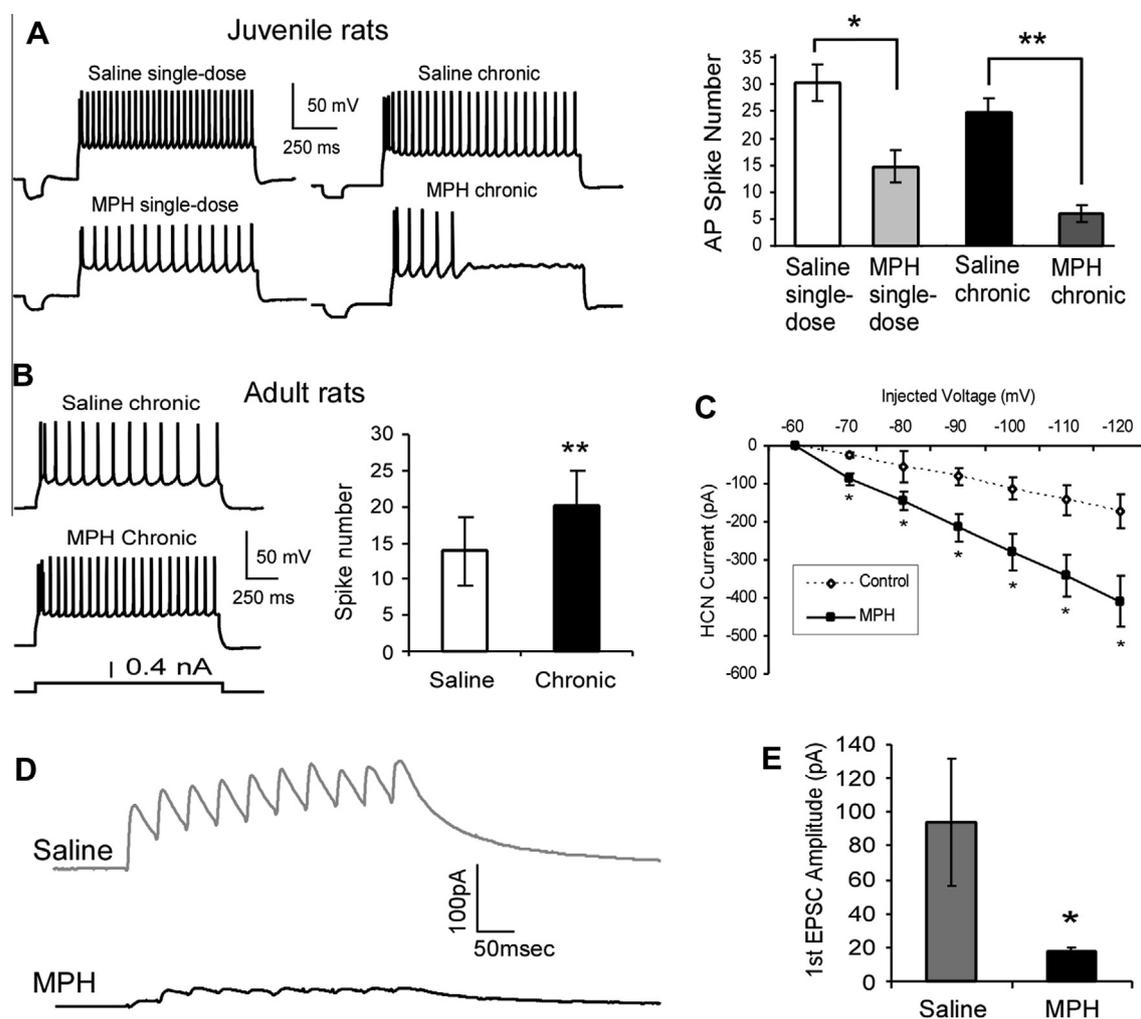


Fig. 2. Age-dependent effects of 1 mg/kg MPH on the neuronal excitability in layer 5 pyramidal neurons in rat prefrontal cortex. (A) Excitability of layer 5 pyramidal neurons in juvenile (postnatal day 15–25) rat prefrontal cortex is suppressed by MPH treatment. Treatment with 1 mg/kg i.p. MPH significantly reduces the excitability (spike numbers) of layer 5 pyramidal neurons in juvenile rat prefrontal cortex. As shown in these representative sweeps, fewer action potentials were observed in single-dose-treated rats than control animals and even fewer in chronic-treated animals. Right panel, summary histogram shows the significant decrease of spike numbers in single-dose ($n = 11$, $p = 0.019$) compared with single-dose saline control ($n = 18$), and even fewer in chronic MPH-treated rats ($n = 18$, $p = 4.58 \times 10^{-5}$) compared to a chronic saline control ($n = 12$). (B) In contrast, neurons from adult rats (postnatal day 90–100) exhibited an increase in excitability following 1 mg/kg MPH treatment ($n = 6$; $p = 0.0006$) when compared to saline control ($n = 6$). (C) Examination of the cAMP-HCN channel-mediated Ih current reveals an increase in Ih current amplitude concurrent with decreased neuronal excitability following 1 mg/kg MPH treatment ($n = 10$) when compared to saline controls ($n = 7$). I/V graph reveals significant increase of Ih current in MPH-treated neurons from -70 mV to -120 mV injected voltage (treatment by sweep interaction, $p = 0.0003$, $f = 5.3$, $df = 5, 75$; treatment effect, $p = 0.0182$, $f = 7$, $df = 1, 15$; injected voltage effect, $p < 0.0001$, $f = 27.4$, $df = 5, 75$). (D) Representative traces of NMDA receptor-mediated EPSCs recorded at $+60$ mV in the presence of picrotoxin ($50 \mu\text{M}$) and DNQX ($20 \mu\text{M}$) in response to a 10-pulse 20-Hz train of stimuli from saline-treated controls ($n = 7$) and MPH-treated neurons ($n = 7$). (E) The amplitude of the first EPSC was significantly reduced in MPH-treated neurons compared to saline controls ($*p < 0.05$; $**p < 0.01$).

potentiation and depression in the prefrontal cortex are unclear, as it is not known exactly what long-term potentiation is representing in this region. However, it might be hypothesized that, if short-term potentiation is a marker of working memory, then long-term potentiation might be a marker of sustained attention and longer-term memory consolidation. Thus, perhaps treatment of the healthy juvenile brain with these low doses of MPH results in impaired working memory and behavioral flexibility, but enhanced sustained attention and long-term memory? If this is the case, it could indicate that MPH-treated children who do not in fact have ADHD would appear successfully treated in a class-room setting – these children would be paying attention to the teacher, less hyperactive and learning might improve; however, stringent testing of their behavioral flexibility and working memory might reveal deficits that could affect other areas of their lives.

Overall, these recent studies suggest that MPH may affect the integration of incoming signals and thus impair working memory function in the juvenile brain. A flowchart demonstrating the differential actions of methylphenidate on juvenile and adult normal brain systems is shown in Fig. 3.

In addition, while it is currently unclear whether the selective decrease in NR2B protein levels indicates a deleterious side effect of treatment, or suggests that ADHD pathology may involve an alteration (presumably an increase) in NR2B levels, what is apparent is that we need to develop stronger diagnostic and treatment measures for ADHD. Currently the diagnosis based on the Diagnostic and Statistical Manual, Version V is subjective, and leaves room for erroneous diagnosis and treatment [75]. Findings such as those presented in the above studies stress the need for the development of more stringent, effective diagnostic and treatment measures that will help to minimize the number of persons needing psychostimulant medication. Furthermore, our studies suggest that children treated erroneously with MPH may be at risk for abnormal

prefrontal function and behavioral plasticity; however, further studies are needed to determine the exact ramifications of the neuronal changes we uncovered following juvenile treatment of healthy rats with clinically-relevant doses of MPH. Our results also suggest that, if the alterations in NMDA receptor composition and plasticity do not turn out to be detrimental to behavioral function, then they likely represent a therapeutic action of the drug. If this is the case, perhaps ADHD is a disorder of glutamate dysfunction, and medications that affect NMDA receptors could provide a future avenue of drug development?

Whether the pharmaceutical companies may develop future ADHD treatments targeting the glutamatergic system, or our findings on NMDAR dysfunction indicate a potentially therapeutic side effect for individuals with ADHD, the fact that even a very low dose of methylphenidate can have such striking effects on developing brains should raise alarm. These age-dependent sensitivities may not only apply to psychostimulants, but to other classes of psychoactive drugs, such as antidepressants and antipsychotics. The take-home message is that, whatever the drug being considered, one must play an active role in researching and understanding the medication, the disease it is prescribed for, and other non-pharmaceutical treatment possibilities. Only then will we, as a society, be able to rest assured that we are not improving children's sustained attention at the expense of other vital cognitive functions.

Conflict of interest statement

We affirm that the content of this manuscript is not under consideration for publication elsewhere. Fig. 2 was derived from two recent publications in the *Biological Psychiatry* and *Neurobiology of Learning and Memory*, which we have obtained permissions from the *Elsevier Publisher* (see the attached permissions). Both authors have fulfilled all conditions required for authorship and have

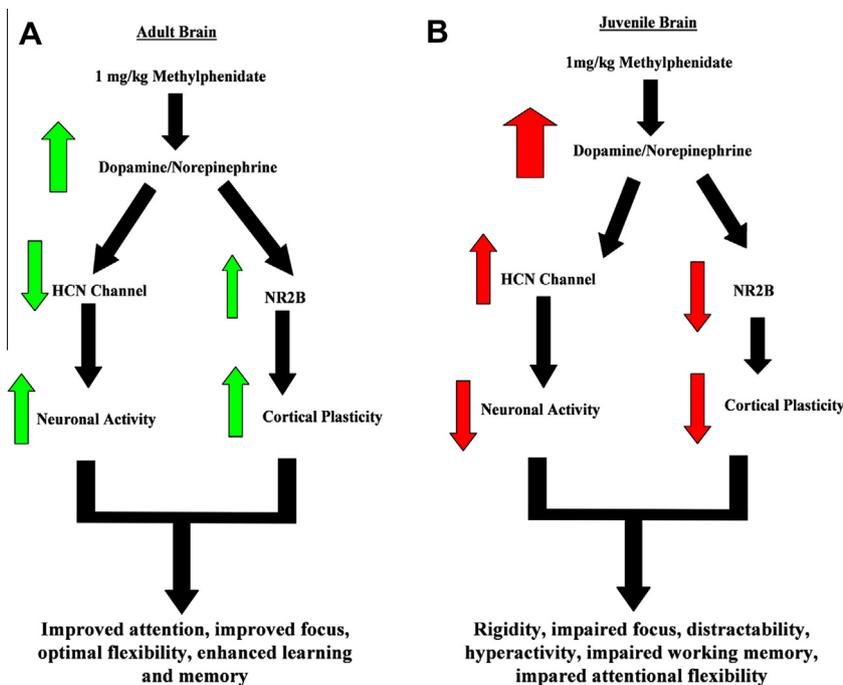


Fig. 3. Flowchart explaining the proposed age-dependent actions of methylphenidate. (A) In the adult brain, MPH causes moderate increase of dopamine and norepinephrine, leading to deactivation of HCN channels and thus increased neuronal activity on one hand, and enhancing NR2B levels through modulation of signal-to-noise ratio to result in increased cortical plasticity on the other hand. These results are beneficial to attentional performance and memory enhancement. (B) However, the juvenile brain is supersensitive to MPH, the same dose of MPH causes excessive levels of dopamine and norepinephrine, leading to activation of HCN channels and decreased levels of NR2B-containing NMDA receptors. These opposite effects result in decreased neuronal activity and impaired cortical plasticity, which, consequently, causes a depression and reduced attention and memory.

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