



*Commentary*

**Neuroenhancement and the Developing Brain: Commentary on the AIMS Neuroscience Special Issue on “Neuroenhancers”**

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**Abstract:** The use of pharmaceutical neuroenhancers to improve cognitive function poses unique neurobiological concerns as stimulants are being widely prescribed to adolescents and young adults with increasing prevalence. In the following commentary on the papers by Hoffman et al [1] and Cheung and Pierre [2] in the special issue on Neuroenhancers, we discuss the need to consider the effects of stimulant use in healthy adolescents. We review some of the data that has emerged on the neurobiological and behavioral effects of adolescent neuroenhancement, and conclude that special consideration should be taken to characterize the consequences of neuroenhancement use in the developing brain. Studies focused specifically on adolescent vulnerabilities to neuroenhancement are necessary because the brain undergoes dynamic changes that are unique to this period of development, which differentiates it from the healthy adult response to neuroenhancer exposure. Moving forward, scientists and physicians should take careful consideration to examine the long-term neurological consequences of neuroenhancers so that the therapeutic benefits that might be gained from neuroenhancement are not shadowed by negative consequences to public health in the future.

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## 1. Introduction

The often-heard assertion that the human brain operates at only 10 percent of its full capacity has been well established as myth [3], but it bears a sentiment that is echoed in the recent emergence of neuroenhancement. The notion that the human brain holds some untapped potential has been met with endeavors to improve normal brain function and cognition using a wide variety of behaviors, dietary supplements or pharmaceuticals [2–6]. In the “Neuroenhancers” special issue, two papers examine the possible benefits as well as the ethical concerns that are being raised by neuroenhancement [1,2]. Hoffman et al [1] review the potential efficacy of cognitive enhancers as supplements to cognitive behavioral therapy (CBT) for patients with diagnosed anxiety disorders. The authors examine evidence that drugs able to acutely enhance learning in the brain could boost the effectiveness of CBT and improve patient outcomes. There is certainly data that does suggest that pharmaceutical stimulants have the capability to enhance cognition in healthy patients (Reviewed in [7]), so it seems quite possible that neuroenhancing adjuvants in CBT represent a new avenue of patient treatment. In summarizing the published data on neuroenhancer efficacy in anxiety disorder treatment, the authors emphasize the need for more studies before neuroenhancers can be fully established as viable therapies. Cheung and Pierre [2] explore the medical ethics associated with the use of prescription drugs for the purpose of neuroenhancement, and present a case study of nonmedical ADHD medication use in order to investigate the ethical considerations of dispensing cognitive neuroenhancers to patients in the absence of a diagnosed illness. Notably, there is no official framework in place to guide physicians through the process of considering the ethics of neuroenhancement. Cheung and Pierre [2] conclude that there does not exist a strong argument for prescribing neuroenhancers to healthy patients. Both articles emphasize what is both enticing and concerning about neuroenhancement, and demonstrate that greater attention to the biological and social implications of neuroenhancement is warranted.

In the following commentary, we turn our focus to the topic of adolescent neuroenhancement use and explore some potential concerns regarding adolescent exposure to prescription stimulants used to treat attention deficit hyperactivity disorder (ADHD). ADHD medications have gained a great deal of attention in recent years for their potential neuroenhancement properties [8]. Commonly prescribed stimulants include the amphetamine-based Adderall® and methylphenidates Ritalin® and Concerta® [9]. Interestingly, methylphenidate is not only the most commonly prescribed ADHD medication but also the most prescribed drug among adolescents [9,10]. Thus, there are broad implications for understanding how methylphenidate affects the adolescent brain. We will discuss the special concerns that should be addressed in the context of brain development and review primary literature examining the effects of methylphenidate on the adolescent brain. We hope to highlight issues that we believe are important to consider moving forward in the realm of neuroenhancement.

## 2. Neuroenhancement and the Developing Brain

The development of the adolescent brain is a process that is characterized by heightened neuroplasticity [11] and structural and functional changes [12,13]. Features such as synaptic density, cellular morphology and neurotransmitter signaling are modified as the brain and its circuits mature [12]. Given the dynamic nature of the developing brain, adolescents engaging in neuroenhancer use may be uniquely vulnerable to pharmacological insults. Recently, it has been reported that prescriptions for ADHD medications among adolescents are on the rise [14,15] and the nonmedical prescription stimulant use by adolescents and college students has become a significant public health concern [14,16–19]. Taking into consideration the widespread use of stimulants by teens and young adults, extra attention should be paid to the potential harms that stimulants could pose to the developing brain. It should also be noted that in addition to potential biological vulnerabilities, adolescents and young adults are often subjected to unique social and cultural pressures that may actuate neuroenhancer use and abuse. For example, among adolescents and college students where the illegal diversion of prescription stimulants has been reported [20,21], academic pressures are often cited as a cause of neuroenhancer use [22]. Furthermore, there is evidence that in addition to nonmedical cognitive enhancement, ADHD medications are being used for recreational purposes on college campuses [23], which is especially troubling since the potential for neuroenhancer addiction has yet to be fully addressed [24]. Thus, neuroenhancer use may expose adolescents and young adults to both short-term and long-term health risks, and its practice maybe be further promoted and perpetuated by their environment. Like known drugs of abuse, neuroenhancers might pose unique threats to the highly plastic adolescent brain and interfere with healthy development.

### 2.1. *Assessing the long-term effects of adolescent neuroenhancement on the brain*

Researchers are beginning to turn their attention to the effect of neuroenhancers on the healthy adolescent brain, though the numbers of these studies remains limited. Rodent animal models have begun to shed some light into how adolescent exposure to methylphenidate (the most commonly prescribed drug and stimulant among adolescents) affects behavior and physiology. Since the adolescent brain is much more plastic than the adult brain, it is reasonable to predict that the developing brain would respond differently to methylphenidate. Not only does evidence support this hypothesis, but it appears that there may also be long-term effects of adolescent methylphenidate use as well. Using healthy adolescent and adult rats, van der Merel et al [25] employed magnetic resonance imaging (MRI) in order to assess changes in connectivity, pharmacological activation, and structure as a result of a 3-week course of methylphenidate treatment. They found that there were structural changes in the brain that occurred only in adolescent rats following methylphenidate treatment. A more recent study examining the hippocampus identified different behavioral and molecular responses to methylphenidate treatment in adolescent rats [26]. Adolescent rats displayed impairments in novel object recognition, significant changes in hippocampal shape and an increase in

neurogenesis that did not occur in adults treated with methylphenidate [26]. Burgos et al [27] found that methylphenidate induced long-term changes in cellular plasticity in rats that received treatment during adolescence. Shortly after administration of high doses of methylphenidate, adolescent rats demonstrate increased learning in a behavioral task that coincides with an increase in long-term potentiation (LTP), a cellular mechanism of learning. However, many months later, the same animals no longer display increased LTP compared to untreated animals. Furthermore, LTP could not be induced by further methylphenidate treatment. This suggests that adolescent methylphenidate treatment can induce long-term changes in the physiological dynamics of the brain long after treatment. Rowan et al., 2015 [28] also showed that adolescent exposure to methylphenidate induces impairments in performance in learning tasks during adulthood, long after the initial drug exposure. This provides direct evidence that cognitive function in later life may be impaired following adolescent methylphenidate use. Finally, further evidence that methylphenidate induces permanent changes was found by Shanks et al., 2015 [29]. They discovered that in female mice, adolescent exposure to methylphenidate caused sensitization to the behavioral effects of methamphetamine administration during adulthood [29]. This data has important implications for neuroenhancer misuse, which has been reported to occur concurrently with other drugs of abuse in college students [23]. By altering the way the brain responds to other drugs of abuse, methylphenidate may have an even broader effect on brain function and health than those related to its immediate interactions in the brain. These results demonstrate that neuroenhancement may have very unique implications for the developing brain and emphasize the need to consider the adolescent-specific effects of ADHD stimulants on brain development and functioning. Neuroplasticity may be an immense strength but also a potential vulnerability of the developing brain that could be commandeered by neuroenhancers. More work needs to be done to understand what changes may be incurred in the brain in healthy individuals taking psychostimulants for neuroenhancement.

### **3. Conclusion**

Expanding the natural capabilities of the human brain is an enticing concept, but it is one that should be approached with caution. The emergence of novel scientific innovations and technological advances has brought about a “neuroscience revolution” [30], in which our ability to examine and manipulate brain functioning is rapidly advancing and improving. Within this context, neuroenhancement poses important social, scientific and health concerns. Of note, the use of stimulants among adolescents and young adults has become a significant issue. We do not yet fully understand the complex dynamics of the developing brain or how the brain responds to chemical intrusions during this period of maturation. Furthermore, the practice of neuroenhancement appears to be persistent among youth, despite the fact that little is known about the potential health risks.

Because our scientific understanding of both acute and long-term physiological and behavioral effects of neuroenhancement in adolescents without diagnosed illnesses is limited, greater emphasis should be placed on studying these effects in the near future. Longitudinal studies focused on

elucidating the influence of neuroenhancement on the developing brain should be a critical component of neuroenhancement research. To counter the paucity of data on human subjects, recruiting efforts could be made on college campuses where research facilities have access to large populations of young adult subjects. From these recruitment efforts, long-term follow-up may be critical to identifying long-term biological effects of neuroenhancement, as measurable changes may not present themselves until much later in life [31]. While there are certainly limitations to studies of pharmacological interventions in healthy human subjects, the continued use of animal models can fill in many gaps in our comprehension of how neuroenhancers affect the brain. By characterizing the neurobiological mechanisms underlying pharmacological neuroenhancement, scientists and physicians can better define the risks involved and establish more informed ethical and medical guidelines for neuroenhancer use. Ultimately, researchers should take an active role in promoting a better understanding of how neuroenhancers affect the healthy brain. We recommend continued evaluation of prescription stimulants and research initiatives that examine the longitudinal effects of neuroenhancement during adolescence and early adulthood. Finally, dissemination of human and animal model data to the general public can raise awareness of the risks that may be associated with nonmedical use of neuroenhancers. This information could potentially discourage illicit neuroenhancement use, particularly while the potential harms and consequences are not yet well understood.

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