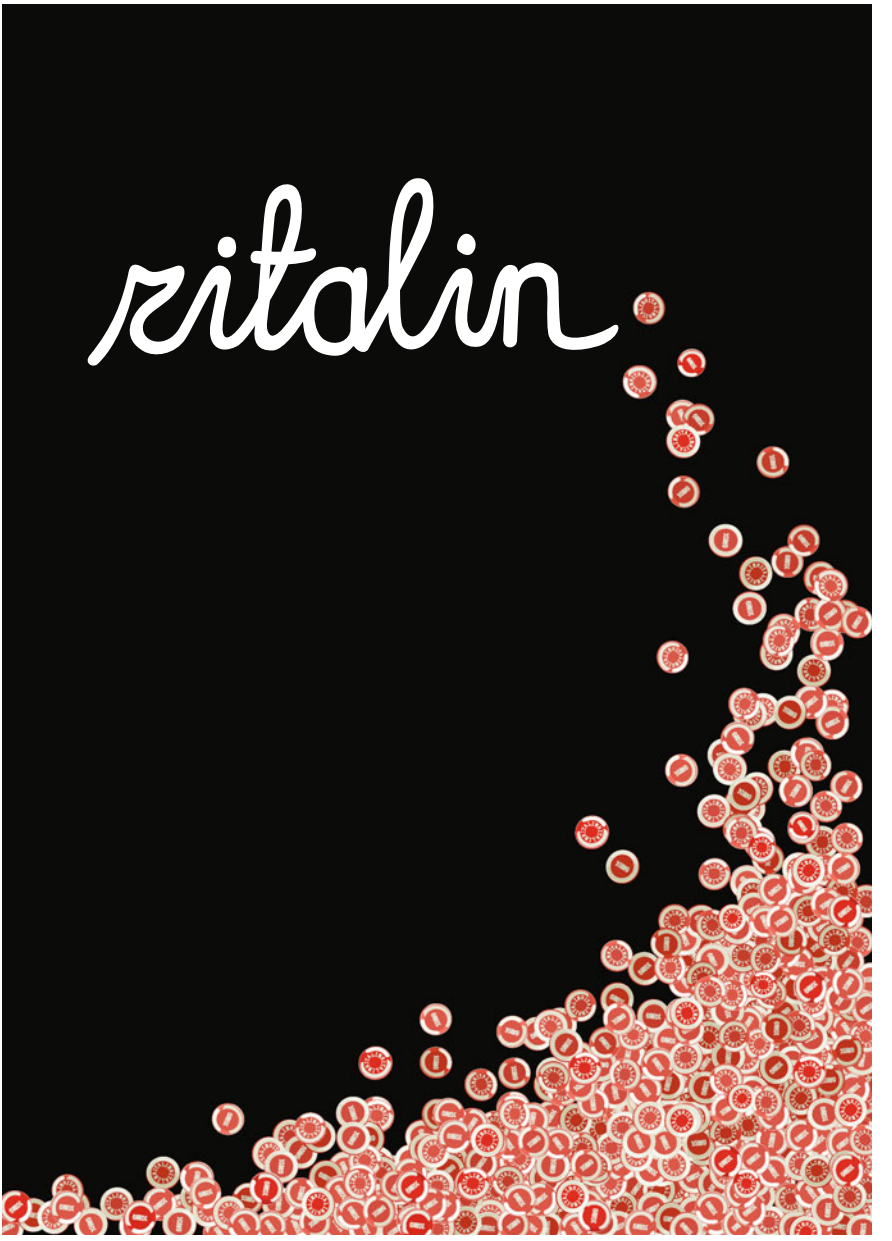
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Ritalin

Lorenza S. Colzato and Fréderique E. Arntz

Introduction

Methylphenidate, best known by its brand name Ritalin, is an amphetamine drug. Ritalin is the most prevalent medication for attention deficit/hyperactivity disorder (ADHD), a well-known psychiatric disorder characterized by hyperactivity and impulsivity. Ritalin increases the availability of dopamine (DA) and norepinephrine (NE) in the brain, especially affecting DA levels (Sulzer et al. 2005; Volkow et al. 2002a, b). DA is a catecholamine that innervates many regions throughout the brain (Moore and Bloom 1978) and is crucial in the regulation of attention and cognitive control (Cools and D'Esposito 2011; Colzato et al. 2010). Furthermore, DA is the precursor of NE so that the availability of DA also influences the NE levels in the brain indirectly. Given that the diagnosis of ADHD and the medical prescription of Ritalin have increased in the past decade, Ritalin has become more easily available to healthy population. Whereas Modafinil (see Chapter "Modafinil") has little evidence of dependence (Jasinski 2000), methylphenidate has a high risk of abuse (Morton and Stockton 2000).

Non-medical use of Ritalin and similar prescription drugs has expanded among healthy adults, especially college students. An "unofficial" way to obtain Ritalin is from family or friends who were prescribed with Ritalin. The most common reasons for trying Ritalin are to concentrate and perform better at work/study, to stay awake

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and to "get high" or to feel good. User statistics of nonmedical use of Ritalin differ widely as there are no official numbers available, because the use of Ritalin without prescription is nonregulated and is considered medication abuse. Therefore, the numbers vary considerably. McCabe et al. (2005) found 4.1% of students using Ritalin in the last academic year. In contrast to this finding, Low et al. (2002) found 35.5% of undergraduate students had used Ritalin as an enhancer in the past year. In another study, 3407 U.S. undergraduate college students were asked about the use of Ritalin in order to improve their cognitive performance (Rabiner et al. 2009). Of this sample 8.9% of the students reported use of Ritalin. Among these users 7.2% was male and 4.5% was female. Consistent with previous findings by McCabe et al. (2005), users were more often Caucasian than of other descendants (Afro-American, Hispanic, Asian). Two other factors that were associated with higher prevalence of Ritalin use were lower grades and membership of a sorority system (McCabe et al. 2005).

Given that Ritalin increases cognitive performance in individuals with ADHD (Mészáros et al. 2009; Faraone et al. 2004), in recent years the interest in the effectiveness of Ritalin as a potential cognitive enhancer in healthy individuals has increased. Unfortunately, the findings of studies investigating these effects have gained inconsistent or even contrasting results. The aim of this chapter is to provide an overview of the "state of the art" of the effects of Ritalin administration on cognition in healthy individuals, thereby clarifying whether it is advisable to use Ritalin as a cognitive enhancer.

In this chapter we will first describe how Ritalin administration affects DA function by taking into account genetic differences associated with baseline DA levels. Second, we will present an overview of the studies investigating the enhancing effects of Ritalin on cognitive functions in non-sleep-deprived healthy individuals. Third, we will review studies that address the effect of Ritalin in sleep-deprived individuals. Studies seem to suggest Ritalin increases working memory only to some extent and especially in challenging conditions.

Mechanisms of Action

Methylphenidate, the active ingredient of Ritalin, is a DA re-uptake inhibitor. That is, it increases DA and NE levels by blocking the transporters of these neurotransmitters (Sulzer et al. 2005; Volkow et al. 2001, 2002b), see Fig. 1. Consequently, because transport of DA is blocked, the amount of DA that is available postsynaptically is increased (Morton and Stockton 2000). The uptake peaks approximately between 60 and 180 min after ingestion, depending on the previously administered dose and individuals' differences in metabolism (Novartis 2016). It is generally recommended to take Ritalin after the consumption of food, as this not only reduces the occurrence of side effects, but also improves the rate at which Ritalin reaches its peak plasma levels (Chan et al. 1983). The effects last from 120 to approximately 240 min (Kimko et al. 1999), also depending on the

dosage and weight of the individual. The half-life of Ritalin is estimated to range around 3.5 h (Novartis 2016). An fMRI study from Volkow et al. (1998) found that peak brain levels are reached after 60 min after oral administration of Ritalin. Methylphenidate is first absorbed in the gastrointestinal tract and from there enters the body's circulation system (Kimko et al. 1999). Methylphenidate can cross the blood–brain barrier by a free diffusion mechanism of nonionized liphophilics. Given these properties, effects of methylphenidate occur shortly after ingestion of the medication (Pardridge and Connor 1973). This results in a rapid effect on dopaminergic supplies in the whole brain, especially increasing DA levels in the prefrontal cortex, which is crucial in the regulation of cognitive control (Cools and D'Esposito 2011; Colzato et al. 2010). The enhancing effects of cognitive control via Ritalin administration are assumed to be related to transporter blockade of the DAD1 receptor and the Alpha-2 adrenergic NE receptor (Spencer et al. 2015).

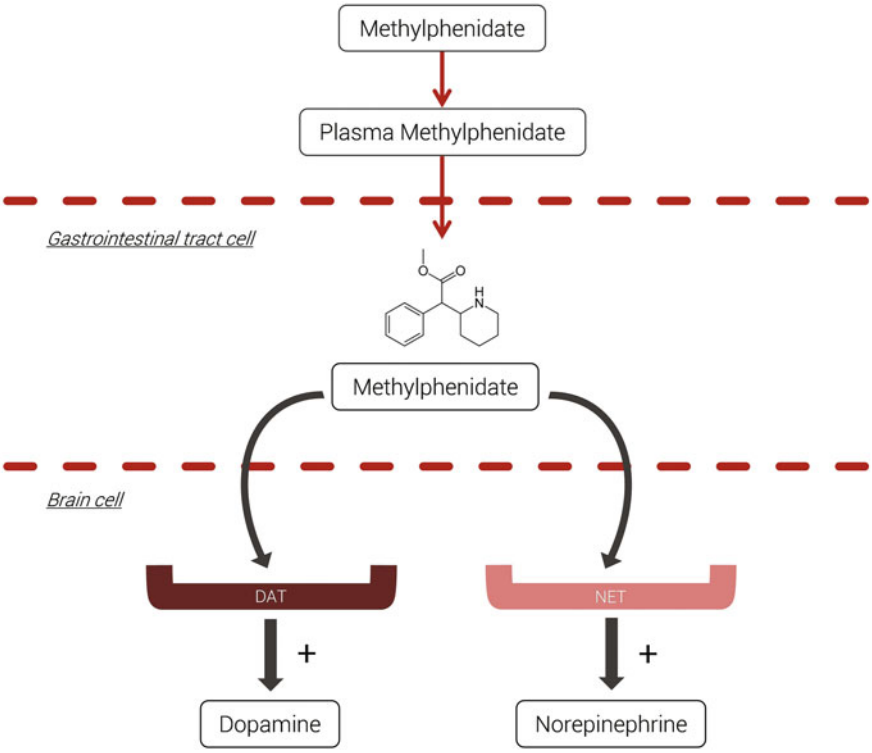

Fig. 1 Schematic representation of Ritalin metabolism. After ingestion Ritalin is absorbed in the gastrointestinal tract, enters the body's circulation system and crosses the blood brain barrier. There, Ritalin leads to blockage of the transporters of both dopamine (DAT) and norepinephrine (NET). This in turn leads to an increase in post-synaptic levels of dopamine and norepinephrine, especially in the prefrontal cortex

The medication has a dose-dependent relationship, with the recommended dose being 10–60 mg a day and the upper daily limit set at 1 mg/kg. This dosage is set for individuals with ADHD via clinical guidelines (Morton and Stockton 2000), however for healthy individuals there is no recommended dose available, as currently the use of Ritalin without prescription is not legal. Most studies investigating the effects of Ritalin on cognition in healthy individuals do not take the dose-dependent relationship into account, and are administering the same dose to all participants regardless of their weight. This methodological fallacy might be one factor contributing to inconsistent findings in the efficacy of Ritalin. Only few studies have taken this factor into account and worked with a mg/kg determined dose, ranging between 0.025 and 0.5 mg/kg (Volkow et al. 1999; Wetzel et al. 1981). Higher doses than 1 mg/kg/daily have been found to have detrimental effects including more pronounced side effects such as: insomnia, loss of appetite, nausea, nervousness, headaches, and high blood pressure (Rapport and Moffitt 2002). Some of the side effects are considered major given that they can cause heart rhythm abnormalities such as arrhythmia, tachycardia, and palpitations (Rappley 1997).

When Ritalin is used repeatedly over time, tolerance (i.e., a diminished response) may develop. Moreover, in contrast to tyrosine (see Chapter "Tyrosine"), the ingestion of a high dosage of Ritalin comes with the risk of overdose. Therefore, it is not surprising that misuse of Ritalin is associated with sudden death (Lakhan and Kirchgessner 2012). Even though for healthy individuals there is no recommended dose available, studies investigating this population typically use dosages between 5 and 60 mg (Repantis et al. 2010). Most studies investigating the enhancing effects of Ritalin administer a dose of 20 mg (Repantis et al. 2010). Beneficial or detrimental effects of Ritalin administration may depend on DA baseline level. These individual differences may be the crucial factor in explaining inconsistent findings of the effectiveness of Ritalin. More specifically, the effectiveness of amphetamines is influenced by genetic differences in a catechol-*O*-methyltranferase (COMT) enzyme (Mattay et al. 2003), which regulates the degradation of DA. This enzyme is genetically coded with two alleles, the valine (Val) and methionine (Met). The presence of a Val allele results in faster degradation of DA than the presence of a Met allele, resulting in less available DA in the brain (Caldù et al. 2007). As DA follows an inverted U-shaped function of effectivity (Cools and D'Esposito 2011), genetic carriers (Val/Val) associated with low DA baseline levels are the ones expected to profit the most from the administration of Ritalin. To date, one seminal study has taken these preexisting individual differences of baseline DA levels into account when investigating the effectiveness of amphetamine in healthy individuals. In an fMRI study, Mattay et al. (2003) explored the effect of the Val^{158}Met polymorphism (COMT gene) on the effectiveness of amphetamine in predicting working memory performance. Importantly, this study showed an enhancing effect of amphetamine administration in a working memory task only for Val/Val homozygotes (i.e., individuals potentially associated with lower frontal DA level). For Met/Met homozygotes (i.e., individuals potentially associated with higher frontal DA level), the amphetamine administration was found to have no effect when the workload of the working memory task was low or moderate and impaired performance at high working memory load.

Even if this hypothesis needs to be formally tested, given that Ritalin is pharmacologically very closely related to amphetamines, we speculate that genetic predisposition might modulate the effect of Ritalin in its role as cognitive enhancer.

Enhancement in Non-sleep-deprived Healthy Individuals

This section provides a summary of recent studies on the effect of Ritalin on healthy adults who are not sleep-deprived. In contrast to the animal literature, findings in humans were mixed. We will discuss factors that may be responsible for the contradictory results.

In animals, a recent review demonstrated a reliable enhancement of cognitive functions after the administration of Ritalin (Spencer et al. 2015). In particular, it seems that, following an inverted U-shaped function logic, low doses of Ritalin lead to improvement of cognitive functions related to prefrontal cortex (Berridge et al. 2006; Gamo et al. 2010). Spencer et al. (2015) suggested that these findings in animals may be translated to humans and, therefore, Ritalin could be regarded as a potential cognitive enhancer for healthy individuals.

Unfortunately, results from human literature do not support this idea and findings in healthy individuals are inconsistent. Ritalin seems to enhance cognitive functions related to memory only to some extent. At short term, a single dose of 20 or 40 mg can significantly augment declarative memory in a word-learning task, while lower doses (5 and 10 mg) induce no beneficial effects (Linssen et al. 2012). Moreover, a double-blind, placebo-controlled study by Camp-Bruno and Herting (1994) reported improved working memory after the ingestion of 20 mg Ritalin only on difficult tasks. Participants were tested 60 min after the administration of the medication. Improvement was found on the difficult task (Buschke Selective Reminding Test) that required selective remembering, whereas no effects on the free recall of words (Immediate and Delayed Free Recall) were found. Another study, employing a single dose of 20 mg, found no impact on the performance of a visual working memory task (Studer et al. 2010). Linssen et al. (2014) analyzed 60 studies in which the participants aged between 18 and 60 years were given a single dose of methylphenidate. Working memory was improved in 65% of the studies, followed by processing speed in 48%. Notably, less behavioral enhancement was evident for attention and vigilance (29%) and the improvement on problem solving and planning was even weaker. In particular the results that Ritalin does not really improve attention are surprising given that many healthy individuals taking Ritalin reported using it to enhance their focus of attention.

Another unexpected result is that even though administration of Ritalin enhanced inhibitory control in people suffering from ADHD (Schachar et al. 2008), this is not the case in healthy individuals. As indexed by the stop-signal task, a single dose of 45 mg did not improve the ability of stopping on time (Manza et al. 2016).

The enhancing effects of Ritalin administration in healthy individuals might not only depend on weight and on genetically determined differences, as discussed in the mechanism of action section, but they seem to depend on gender as well.

Women experienced more pronounced methylphenidate effects (Davis et al. 2012). These differences might arise from fluctuations in DA associated with the menstrual cycle, possibly due to estrogen. In line with this idea, D2 receptor availability varies according to the menstrual cycle (Czoty et al. 2009) and it has been proposed that cognitive functions associated with DA may depend on estrogen level (Colzato and Hommel 2014; Jacobs and Esposito 2011).

In sum, in healthy non-sleep-deprived individuals, Ritalin appears to increase working memory only to some extent and especially in challenging conditions.

Enhancing Effect in Sleep-Deprived Individuals

Because of its ability to increase wakefulness, in this section we will describe the only two studies exploring the effect of Ritalin on cognitive functions in sleep-deprived, but otherwise healthy adults. In contrast to the reliable effect of (see Chapter "Modafinil"), the few studies investigating the enhancing effects on cognition after sleep deprivation report inconsistent findings, with one study showing beneficial effects whereas the other failed to find any effects.

In a randomized, double-blind, placebo-controlled study, Bishop et al. (1997) found enhancing effects of repeated administration of a single dose of 10 mg Ritalin after 24 h of sleep deprivation. Ritalin was administered 2 h before testing, with an interval of 4 h in between doses. Results showed that Ritalin led to improved attention and vigilance performance. Furthermore, participants reported to be less tired and this increased alertness was supported by improvement on physiological measures of sleepiness. The alerting effect of Ritalin lasted up to 4 h after ingestion.

In contrast to the previous findings, Bray et al. (2004) found no enhancing effects in a randomized, double-blind, placebo-controlled study, where the effects of 20 mg Ritalin on verbal learning and executive functioning were tested after 24 h of sleep deprivation. The only notable effect that emerged was impairment of self-monitoring. That is, participants showed an overconfidence effect: their perceived performance was better than their actual performance on the tasks.

In sum, Ritalin does not seem to consistently enhance performance after sleep deprivation. The preliminary evidence that is available from the few studies that were carried out does seem to suggest an improvement of attention and vigilance of Ritalin administration after sleep deprivation, but at the cost of overconfidence.

Conclusion

As Ritalin increases DA levels in the prefrontal cortex, it has the potential to improve cognitive functioning. However, current research has found contradicting or inconsistent results. In non-sleep-deprived individuals, beneficial effects of moderate doses of Ritalin have been found on memory performance, but only to

some extent and especially in challenging conditions. It remains to be established whether these findings apply to the long-term administration of Ritalin. Hence, future studies assessing the impact of chronic Ritalin use and the risk of incurring potential side effects are necessary. Indeed, it needs to be clarified whether tolerance or even decline in performance will be encountered after the initial short-term enhancing effects on memory. Moreover, optimal protocols of administration in healthy individuals (e.g., dose of Ritalin dependent on weight, DA baseline levels and gender) still need to be identified.

Future studies need to shed light on whether the efficacy of Ritalin on working memory indeed depends on genetic markers of dopaminergic function. Given that Ritalin increases DA level in the brain, we speculate that Ritalin can promote cognitive performance whenever one has a lower than-optimal DA level. That is, depending on the initial DA baseline levels, some people may benefit more from Ritalin intake than others. This might explain why previous outcomes were mixed: some studies reported significant improvements, while others did not.

Further, more research is necessary in order to establish whether Ritalin has reliable enhancing effects after sleep deprivation as only few studies have addressed this topic.

In sum, considering the side effects and the abuse liability associated with Ritalin, the use of this drug does not seem to reliably enhance cognitive processes except working memory.

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