Methylphenidate and cognitive performance

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Abstract

Methylphenidate (MPH) is the active ingredient of stimulant drugs that are frequently prescribed to individuals with Attention Deficit / Hyperactivity Disorder (ADHD). In this chapter we examine the effect of MPH on different aspects of cognitive performance. The reviewed findings suggest that MPH effectively enhances sustained attention, response inhibition, and working memory capacities; yet not only for individuals with ADHD, but also for those without ADHD. Individuals who seem most affected by MPH are those with a profile of low task performance in the given task. This occurs most strongly under challenging task conditions. We further review the long term consequences of chronic usage of MPH. The findings concerning this issue are less conclusive, but there is no evidence of considerable physical harm or risk of subsequent abuse as long as dosage remains low. Still, the beneficial effects of taking MPH seem to be limited to the treatment period.

Keywords: ADHD, Methylphenidate, Ritalin, Concerta, Cognition, Attention, Drug abuse

List of abbreviations

ADHD - Attention Deficit / Hyperactivity Disorder

AMPA - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid

CANTAB - Cambridge Neuropsychological Test Automated Battery

fMRI - functional Magnetic Resonance Imaging

MPH – Methylphenidate

MTA - Multimodal Treatment of ADHD

NMDA - N-methyl-D-aspartate

OROS MPH - Concerta

TOVA - Test of Variables of Attention

MANOVA - Multiple Analysis of Variance

HIV - Human Immunodeficiency Virus

Methylphenidate (MPH) is a common medical treatment for ADHD (Spencer et al., 1996) and its neuro-cognitive effects were extensively studied in both adults and children with ADHD. These studies showed that MPH improves various cognitive measures such as sustained attention, response inhibition, and working memory (for but a few examples, see Turner, Blackwell, Dowson, McLean, & Sahakian, 2005; Kurscheidt et al., 2008; Agay, Yechiam, Carmel, & Levkovitz 2014). On the other hand, its rising popularity among non-clinical populations, such as students (Bogle & Smith, 2009) may suggest that MPH is a cognitive enhancer and that its beneficial effects are therefore not specific to ADHD. Evidence for the wide non-medical use of MPH was provided by an online poll conducted by Nature magazine in 2008, in which 12.4% out of 1,400 responders reported using MPH for non-medical reasons, such as for improving their ability to concentrate and focus (Repantis, Schlattmann, Laisney, & Heuser, 2010). Indeed, in order to understand MPH's mechanism of action trials with healthy volunteers have been carried out as well, and some of them suggested that MPH is capable of enhancing certain aspects of cognitive performance of healthy adults, working memory for example (Elliott et al., 1997; Mehta et al., 2000).

In the present review we address the following general questions which the existing studies now seem capable of answering. 1) What aspects of performance does MPH improve? 2) Is the effect of MPH selective to individuals with ADHD or is it a generic cognitive enhancer? 3) Are there certain individuals (other than those with ADHD) who may benefit from MPH more than others, and are there conditions where the effect is larger/smaller? 4) Are there any long term consequences or adversities owing to the chronic usage of MPH? In addition, we examine the significance of the

risk of succumbing to other psychoactive drugs as a result of using MPH as well as its potential for curbing substance abuse.

1. Aspects of Performance Affected by MPH

MPH's mechanism of action has been previously suggested to be due to an adjustment of neurotransmitters level: it increases extra-cellular levels of dopamine and norepinephrine by blocking their respective transporters. Dopamine and norepinephrine reduce background firing rates of neuronal cells, thus decreasing non-task related activity and improving signal to noise ratio (Volkow, Fowler, Wang, Ding, & Gatley, 2002; Volkow, Wang, Fowler, & Ding, 2005). Imaging studies of healthy volunteers show that when performing a cognitive task, MPH *decreased* both the magnitude of brain activation and the extent of the regions activated, thus creating a more focused activation pattern (Mehta et al., 2000; Volkow et al., 2008). This is also reflected in a reduction in whole-brain glucose metabolism, compared to the same task performed on placebo (Volkow et al., 2008). However, this effect was found to be dependent on the extent of baseline activation and performance level; in participants for whom the task did not demand high activation on placebo, the effect of MPH on brain activation was not significant, and performance did not improve as well (Volkow et al., 2008). Another imaging study found that while performing cognitive tasks on MPH, activation of the Dorsal Attention Network was increased, while activation of the Default Mode Network, associated with mind-wandering, was decreased (Tomasi et al., 2011).

Recently it has been pointed out that MPH also affects the glutamate system (Urban, Li, & Gao, 2013) by reducing glutamatergic receptor-mediated synaptic plasticity. The glutamate system regulates the plasticity of the prefrontal cortex via

AMPA and NMDA receptors (Lee & Kirkwood, 2011). This effect, which may be due to the hyperdopaminegic state induced by MPH (Urban et al., 2013), was argued to represent a "deleterious side effect" (Urban et al., 2013; p. 73) of treatment. It thus remains in the hand of empirical studies to investigate which of these effects of MPH bears a stronger relevance to cognitive performance in a variety of domains, both in the short and in the long term.

Historically, after MPH was first synthesized by Ciba-Geigy Pharmaceutical Company under the brand name "Ritalin", it was marketed as a treatment for a variety of disorders, including depression, chronic fatigue, narcolepsy, and Mohr's Syndrome (Physicians Desk Reference, 1956). Mounting evidence have shown that MPH improves a variety of cognitive aspects related to ADHD, including sustained attention, response inhibition, and working memory (see review in Leonard, McCartan, White, & King, 2004; and see below). Hence, it became considered as a drug of choice for individuals with ADHD (Schwartz & Cohen, 2013). This is in line with the conceptualization of ADHD as a neurological disorder in which the dopaminergic system is abnormal, and dopamine levels in prefrontal brain areas are lower than expected.

Within individuals with ADHD, MPH was found to improve performance in tasks requiring sustained attention (e.g., Tucha et al., 2006; Kurscheidt et al., 2008; Turner et al., 2005; Agay, Yechiam, Carmel, & Levkovitz, 2010; 2014) as well as retaining and manipulating information during a short period of time (Biederman et al., 2008; Agay et al., 2010; 2014), an ability often attributed to working memory (Klinberg, Forssberg, & Westerberg, 2002). No or very limited effects were found for decision making ability (Agay et al., 2010; 2014; Shalev, Gross-Tsur, and Pollak, 2012; though see DeVito et al. 2008 for different results). Studies have suggested that

these effects may extend to complex real world tasks. For example, in driving, positive effects of MPH were found for speeding and variability of steering, as well as for using turn signals (e.g., Cox, Humphrey, Merkel, Penberthy, & Kovatchev, 2004; Barkley, Murphy, O'Connell, & Connor, 2005).[1]

For healthy individuals as well, it was found that MPH results in improvement in sustained attention (Elliot et al. 1997; Cooper et al. 2005). Two interesting exceptions should be mentioned. A study by Shalev et al. (2012) examined the effect of a single dose of MPH on medical students' performance in a sustained attention task (the Test of Variables of Attention) which is often used to assist in determining ADHD diagnosis. Forty-five students performed the task either on placebo or after taking MPH. Shalev et al.'s results showed no significant effects of MPH on task performance. Their main analysis, however, was a Multiple Analysis of Variance (MANOVA) across several dependent measures. A look at specific error rates (see Figure 1) shows a remarkable effect of MPH on omission errors in their study: the rate of errors in the placebo condition was in some blocks over five times than with MPH.

A smaller-scale study that did not find a linear effect of MPH on sustained attention in healthy children was conducted by Vaidia et al. (1998). The authors' main aim was to investigate how children with ADHD differ from children without ADHD in frontal-striatal brain function and in its modulation by MPH. The study included ten male children with ADHD (mean age 10.5) and six healthy male children as a control group. The main dependent measure was a Go/No-Go task similar to the TOVA, consisting of alternating Go blocks ("press for all letters") and No-Go blocks

[1] It is worth noting that not all participants improve with MPH. There are "non-responders" who do not exhibit cognitive benefits with the drug (Leonard et al., 2004).

("do not press for 'X' "). In the easier "No-bias" version of the task, there were six Go responses in each Go block, and six No-Go responses in each No-Go block. In the "Go-bias" version there were 12 Go stimuli on each Go block versus only six stimuli in each No-Go block, which created a bias towards "go" responses in this version (and increased the rate of commission errors). Accuracy in the Go blocks was 100% in both groups, so the main performance measure was the number of commission errors on the No-Go blocks.

The results showed that in the No-bias version, MPH did not cause a modulation of baseline (off MPH) brain activation in healthy controls, and improvement in performance was specific to the ADHD group. However, in the more demanding Go-bias version, MPH enhanced performance of both groups to the same extent. Thus, a necessary condition for the effect of MPH on healthy individuals appears to be the task difficulty level (this is also consistent with the cortical effects of MPH found in Volkow et al., 2008). Apparently, some tasks do not challenge attentional capacity to a sufficient extent so as to trigger the effect of individual differences in the ability to sustain attention and inhibit unwanted responses.

Interestingly, there are various reports showing that MPH also improves other aspects of behavior for certain clinical populations. In a recent meta-analysis (Candy, Jones, Williams, Tookman, & King, 2008) MPH was found to reduce depression symptoms beyond placebo, but the effect size was small. Still, some specific patient groups show substantial improvements in mood with MPH (as detailed in Leonard et al., 2004). This includes stroke patients, cancer patients, individuals with HIV, and those suffering secondary depression due to surgery or medical illness (Leonard et al., 2004). MPH is also commonly used for treating narcolepsy, though this requires very

high doses (Czeisler, Richardson, & Martin, 1994), and it was found to be effective in the management of comma (as reviewed in Leonard et al., 2004).

In patients with traumatic brain injury, MPH was found to improve various facets of cognitive performance, including sustained attention and working memory capacity (e.g., Silver, McAllister, & Arciniegas, 2009) as well as verbal fluency and decision making (e.g., Mooney & Haas, 1993). Similar improvements were found in cancer patients receiving subcutaneous narcotics (e.g., Bruera, Miller, Macmillan, & Kuehn, 1992) and survivors of childhood cancer with learning impairments (Conklin et al., 2007).

Most remarkably, MPH was also found to improve motor functions in several subgroups, such as the elderly. Studies of relatively healthy elderly adults found that MPH resulted in improved mobility (e.g., mean stride time) and gait (e.g., stride time variability) (Ben-Itzhak, Giladi, Gruendlinger, & Hausdorff, 2008) as well as improved ability to maintain walking and postural stability (Shorer, Bachner, Guy, & Melzer, 2013). A positive trend was also observed in Parkinson's patients (e.g., Moreau et al., 2012).

2. Is MPH an ADHD Treatment or a Cognitive Enhancer?

The straightforward way to examine the specificity of the effect of MPH to individuals with ADHD is to compare the effect of MPH in two groups of participants – ADHD and non-ADHD – with similar demographic indices (e.g., age, gender, education), in a two-by-two research design. Surprisingly, to our knowledge only three studies employed such a comparison; one compared children with ADHD versus healthy children on and off MPH (Vaidya et al., 1998) and the others focused on adults, with and without ADHD (Agay et al., 2010; 2014).

As noted above, Vaidya et al. (1998) compared response-inhibition performance in children with ADHD versus healthy children on and off MPH. Their main results showed that MPH only had selective effects in a relatively easy task condition, whereas in a more demanding condition the effect was evident in both groups. The difference between conditions might have occurred due to a ceiling effect for the easier condition.

In Agay et al. (2010) we examined a larger sample of adults (32 with ADHD and 26 controls) using the TOVA and other cognitive tasks. We compared the effect of a single 15 mg dose of MPH on adults with ADHD and on healthy adults. In each group, half of the participants received MPH and half received placebo. The four sub-groups were carefully matched for age, gender, and years of education.

Participants performed the TOVA test twice: at baseline and after drug administration (either MPH or placebo). Regarding the overall score after drug administration (see Figure 2 top panel), no effects of MPH or diagnosis were revealed, presumably because of a significant practice effect that masked any other effect (baseline scores are not presented in the figure for the sake of conciseness). However, when analyzing the response accuracy measure (d-prime) alone, the results resemble Vaidya et al.'s (1998) findings: There was a main effect of MPH ($F(1,53) = 3.51$, $p = 0.067$) but no interaction with ADHD. As shown in Figure 2 bottom panel, MPH caused greater improvement than placebo in a non-selective manner, that is, similarly in both groups (scores were raised by 15.8% for ADHD individuals and by 11.9% for healthy controls).

In Agay et al. (2010) we further examined whether MPH has a selective effect on performance in tasks assessing working memory capacity. In this study the examination of working memory capacity was constrained to the use of the digit span

task, thought to examine verbal working memory. The results again showed a significant main effect of MPH, with healthy control and people with ADHD alike recalling more digits on average than participants on placebo. The improvement level was higher for those with ADHD than those with no ADHD (20% versus 5%) but the noise in the former group was also higher, such that there was no interaction between ADHD diagnosis and the effect of MPH.

In an attempt to verify that the findings of Agay et al. (2010) are not due to some bias associated with the allocation of participants to the MPH and placebo groups, we conducted a second study employing a within-subject design similar to the one used by Vaidya et al. (Agay et al., 2014). Twenty participants diagnosed with ADHD and 19 healthy controls matched for age, gender, and education were recruited. Participants arrived at the laboratory for two sessions separated by at least one week. On each session they received either a capsule containing 20 mg of MPH or placebo in a double-blind manner. Following pill administration, participants performed a battery of computerized tasks, including the TOVA, the digit span task, and also the spatial working memory task from the CANTAB battery of cognitive assessment, which is often used in the literature on ADHD. The results replicated those found by Agay et al. (2010). There was no ADHD-specific effect of MPH in any of the cognitive tasks: MPH resulted in improved performance relative to placebo in the sustained attention and working memory tasks, both in the ADHD and non-ADHD groups.

What do these results imply? Do they suggest that MPH should not be given to children and adults with ADHD? The answer to that is a clear “no”. Instead, these results suggest that 1) any individual, with or without ADHD, who for some reason finds it difficult to concentrate and as a result performs poorly on some task, may

benefit from MPH. This difficulty may be due to either an attention deficit, stress, or over-concern with off-task matters. 2) An individual with ADHD who masters a certain task and performs well is not necessarily going to benefit from MPH on this particular task. Empirical evidence supporting these two implications are presented in the next section.

Despite these findings many clinicians still share a belief that MPH has negative effects on sustained attention and working-memory related capacities of healthy individuals without ADHD. Is there some support to this idea? The only study that we could detect is that of Clark, Geffen, and Geffen (1986) who administered MPH intravenously to 12 healthy volunteers, who then performed a dichotic listening task. Ten minutes following MPH administration, participants exhibited more talkativeness; and some mentioned that the urge to talk was difficult to restrain. However, this effect may appear in individuals with ADHD as well. Indeed, in a study of children with ADHD Borcherding, Deysor, Rapoport, Elia, and Amass (1990) noted that most participants exhibited abnormal movements, perseverative/ compulsive behaviors, or both, some time during MPH treatment. One explanation for this phenomenon is the rate-dependent effect of MPH, and stimulants in general, upon behavior (Teicher et al., 2003): stimulants exert behavioral effects that are inversely correlated with the baseline rate of behavior. That is, in hyperactive individuals they tend to reduce activity level, whereas in individuals whose rate of activity is low to begin with, they may increase it. Does this effect hold regarding cognitive performance as well? This question leads us to the next section.

3. Who Benefits from MPH and under What Circumstances?

The effect of MPH on cognition is mediated by variables associated with the drug properties, the user, and the task. Like other psychoactive drugs, dose is a critical variable determining the effect upon cognition: low doses of MPH are associated with cognitive enhancement, whereas high doses can lead to euphoria, aggression, addiction, and psychosis. This relationship between dose and cognitive effect of psychostimulants is often depicted as an inverted U-shaped curve (Wood, Sage, Shuman, & Anagnostaras, 2013).

Baseline performance level is also highly associated with the beneficial effect of MPH. Again, a variety of theories proposed an inverted U-shape relation between the administration of MPH and performance level (e.g., Dews & Wenger, 1977; Robbins & Sahakian, 1979; Mehta & Riedel, 2006). Under this general account MPH affects performance mostly when initial performance level is low and its effect reduces as a function of increased baseline performance. Moreover, beyond a certain performance level, it has a negative effect. In support of the notion that the effect of a drug is non-linearly related to individual baseline variables, the dopamine receptor agonist bromocriptine was recently found to have a positive effect on reversal learning performance in individuals with low baseline striatal dopamine synthesis but a negative effect for those with high synthesis capacity (Cools et al., 2009).

An alternative prediction is that while the effect of MPH is performance dependent, with more positive effect for poor task performers, there is no negative effect of MPH for high performing individuals (Agay et al., 2014). This is based on the notion that when the ability to perform a given task is high, task performance is relatively automatic and requires less cognitive control (Ackerman, 1987), thus being relatively unaffected by baseline level of dopamine and norepinephrine. This idea is

supported by studies showing that individuals with low baseline capacities were more likely to improve their performance with MPH than those with higher baseline capacities. This was found both for working memory functions (Mehta et al., 2000; Finke et al., 2010; though see Mehta & Riedel, 2006 for different results), motor functions (Robbins & Sahakian, 1979), and decision making (Zack & Poulos, 2009). Yet these findings are also consistent with the U-shape account.

In Agay et al. (2014) we directly tested these two accounts by studying the correlation between the effect of MPH and performance, in individuals whose performance was improved or impaired by MPH. Participants performed a variety of cognitive tasks including the TOVA, working memory, and decision making tasks twice, on placebo and on MPH. The main results showed that among individuals whose performance improved with MPH (relative to placebo), those that benefited more had lower baseline performance (on placebo) on the same task. In other words, the magnitude of improvement with MPH was inversely correlated to performance level on placebo. This was found for the TOVA task (a correlation of $r = -0.46$, $p = 0.03$ between baseline performance and improvement with MPH), as demonstrated in Figure 3; for the Forward Digit span task ($r = -0.57$, $p = 0.008$), and for the Spatial Working Memory task ($r = -0.78$, $p < 0.001$). By contrast, for those individuals whose performance dropped in the MPH condition, there was no correlation between baseline performance level and the magnitude of the drop in any of these measures.

Additionally, in the Iowa Gambling task (Bechara, Damasio, Damasio, & Anderson, 1994), a repeated complex decision making task (see review in Yechiam, Busemeyer, Stout, & Bechara, 2005), we also observed that individuals who benefited from MPH tended to be those with a lower baseline score ($r = -0.47$, $p = 0.04$), as shown in Figure 4. Additionally, though, in this task those who performed worse with

MPH tended to be individuals with higher baseline performance ($r = -0.72$, $p < 0.001$). This dual effect may be due to a "U shape" effect of MPH on performance, or it could be the result of a regression to the mean (Teicher et al., 2003). Regression to the mean implies that a person who scores low/high in a certain test (e.g., on placebo) is more likely to score closer to the average in another test of the same capacity. Note though, that the regression-to-the-mean pattern, whereby individuals with poor baseline improve with MPH but those with high baseline score less with MPH, was only observed for the IGT. For the remaining cognitive tests in Agay et al. (2014), the results mostly showed the former but not the latter pattern.

Thus, the findings of Agay et al. (2014) suggest that individuals who markedly benefit from MPH in tasks requiring sustained attention and working memory, tend to perform relatively poorly in those tasks without MPH. By contrast, interestingly, there is no consistent evidence suggesting that individuals who perform very highly in these tasks show impaired performance as a result of using MPH (Agay et al., 2014).

Note that the effect of MPH on low-level performers may give rise to an illusion that the drug is ADHD-specific if there is a tendency of people with ADHD to perform more poorly in a given domain (as show in Figure 5). When a target population diagnosed with a certain disorder performs poorly, then the effect of the drug on poor performers in general is confounded by the diagnosis, making it difficult for clinicians to discern these two factors.

As noted above, the positive effect of MPH on performance holds as long as the task is challenging enough so as to trigger relevant individual differences in baseline attentional capacity (Vaidya et al., 1995). Another condition where MPH may be less effective is sleep deprivation. While the indirect-acting dopamine receptor agonist modafinil was found to enhance cognitive processing of sleep-

deprived individuals (Wesensten, 2006), there is no definite evidence that MPH also enhances cognition among sleep-deprived individuals (Bray et al., 2004; Repantis et al., 2010). This result was also replicated in rats (Volkow et al., 2012). Interestingly, sleep-deprived rats showed no increases in dopamine with MPH, but showed similar receptor changes to those observed for wakeful rats. The authors suggest that this may be due to an interaction between adenosine and dopamine following sleep deprivation (though this was not directly tested).

4. Long Term Effects of MPH

Does MPH improve cognitive functioning of individuals with ADHD in the long-term? There is no definite conclusion. There are some reports of improvement in IQ scores (Zhang, Jon, & Zhang, 2011) and in TOVA measures (Huang, Wang, & Chen, 2012) after 6-12 and months of treatment with MPH, but the latter did not use a control group, so that the observed improvement can be attributed to cognitive maturation that is typically expected in children, and not only to the long term effects of MPH treatment. Some long-term effects of MPH treatment on brain activation were reported in an fMRI study of children with ADHD, though with a small sample (Konrad, Neufang, Fink, & Herpertz-Dahlmann, 2007).

A recent study assessed cognitive performance of adolescents with ADHD before and after one year of treatment with extended-release MPH (OROS MPH). At baseline, the ADHD group was significantly impaired in several CANTAB tasks, including spatial working memory, planning, and set shifting, compared to the non-ADHD age and gender matched control group. After one year of treatment, these differences were no longer evident. However, practice effects and placebo effects might partly account for the results (Hammerness et al., 2014).

A multi-site longitudinal study that did use appropriate clinical control and randomized participant allocation was conducted by the Multimodal Treatment of ADHD (MTA) Cooperative group (MTA, 1999). In this study, 579 children diagnosed with ADHD were randomly assigned to one of the following four conditions: (a) systematic MPH medication management, which used initial placebo-controlled titration, with a thrice-daily 7-days per week medication regime, (b) multicomponent behavior therapy, including 27 sessions of parent training supplemented with eight individual parent sessions, an 8-week summer treatment program, 12 weeks of classroom administered behavior therapy, and 10 teacher consultation sessions, (c) their combination, or (d) usual community care. The results showed that after 14 months all groups showed improvement compared to baseline in ADHD symptoms and related cognitive tests. However, the MPH therapy and the combination of MPH and behavioral therapy induced the largest improvements.

Molina et al. (2009) continued to track the MTA study participants for an additional 8 years, and compared them to a group of 261 non-ADHD peers. The results showed that the initial effect of MPH tended to wane over time (as well as the effects of the psychosocial treatment). The substantial effects MPH treatment had produced over the treatment period of 14 months were not maintained during the following years, when treatment regime involved routine community care. After these 8 years, there were no significant differences in cognitive performance between those initially treated with MPH and those who were not. Thus, there was no indication that MPH had any long term effects.

Does exposure to MPH in childhood and adolescence have long-term harmful consequences upon the developing brain? Due to ethical and practical considerations this was mainly investigated in animal studies. Primate studies have shown that

chronic use of MPH in clinically relevant doses, starting from pre-adolescence, does not alter the development of the dopamine system, does not affect physical growth, does not cause hyper-sensitivity to cocaine, and does not impair motor/cognitive behavior after treatment end (see review in Volkow, 2012). Most recently, a study of 340 children with ADHD and 680 without the condition showed that stimulant medications were not associated with indices of growth and final height (Harstad et al., 2014).

Extensive amounts of MPH can, however, lead to psychologically devastating effects. In a small-scale study, Pawluk, Hurwicz, Schluter, Ullevig, and Mahowald (1995) examined a group of 11 narcolepsy patients who had received doses of methylphenidate in excess of 100 mg/day for at least 5 years immediately prior to the study. This amount exceeds the normal dose administered to people with ADHD by about 3-5 times. They found that while only one of these patients suffered major depression (and this might not have been due to the stimulant), two of the patients had symptoms of MPH-induced psychosis.

5. Applications to Other Addictions and Substance Misuse

Chronic use of MPH has been suspected to be associated with substance use. This is because MPH elevates dopamine levels in the nucleus accumbens, a pharmacological effect similar to drug reward; repeated use may trigger dopaminergic and glutamatergic signaling associated with addiction (Volkow, 2012). Indeed, animal studies have shown that exposure to MPH, especially in adolescence, produces effects that are related to substance use, such as a later preference for cocaine (Humphreys, Eng, & Lee, 2013). Likewise, some studies reported increased risk for cigarette smoking and substance use problems in MPH-treated participants with ADHD

(Lambert & Hartsough, 1998). By contrast, several longitudinal studies reported that MPH treatment actually protects against substance abuse later in life (Kollins, 2007). A recent meta-analysis of 15 longitudinal studies with 2,565 participants assessed abuse or dependence status for alcohol, cocaine, marijuana, nicotine, and nonspecific drugs, and concluded that stimulant treatment neither protects nor increases the risk for substance use disorder later in life (Humphreys, 2013).

MPH is considered to have a potential for abuse, or abuse liability. One method to assess abuse liability is by measuring subjective (self-reported) effects of the drug, such as drug liking, euphoria, etc. Studies in healthy volunteers show that MPH produces a subjective effect indicative of abuse liability (Kollins, 2007). For example, in a study of six participants with histories of cocaine use, the subjective effects of MPH (15-90 mg) were similar to those of oral cocaine (50-300 mg) across a range of doses tested (Rush & Baker, 2001). The authors note that this may be indicative of an abuse potential of MPH (but see the remarks below).

However, participants with ADHD do not experience these subjective effects, and this is consistent with the fact that many of them do not like taking their medication due to a disphoric feeling they often report. This implies that the abuse potential may be lower in individuals with ADHD than in those without ADHD. (Kollins, 2007).

Another method to assess abuse liability is testing whether the drug has a reinforcing effect. Such effect has been observed in participants with ADHD, who preferred MPH over placebo in a repeated choice procedure. However, this effect was associated with the clinical effectiveness of MPH compared to placebo rather than with abuse liability, as evidenced by the participants' subjective reports. It should be noted though that a) abuse liability as measured in the lab does not always translate to

actual drug abuse outside the lab; whether or not a drug will be abused is more strongly determined by various environmental factors (Carter & Griffiths, 2009). For example, in the above study of Rush and Baker (2001) comparing MPH and oral cocaine, the authors note that despite the similar behavioral-neuropharmacological profile of these two drugs, epidemiological data shows that their rates of abuse are different (cocaine being more often abused than MPH). b) these experiments used immediate release MPH. The abuse liability of extended-release formulations, which are widely used nowadays for ADHD treatment, has been studied less, but there are indications that they have lower abuse potential among non-ADHD individuals (Kollins, 2007).

When discussing the abuse potential of a drug, is it important to distinguish between drug abuse, which is chronic use that leads to significant impairments in major life domains and to legal and interpersonal problems, and misuse, which is simply a non-medical use that rarely leads to such impairments. Evidence of MPH abuse are relatively rare, and are usually observed in specific populations (like methadone users) or in intravenous administration. Dependency or addiction to stimulants that are used for ADHD treatment is rarely observed in clinical practice or in the literature. Misuse and diversion, on the other hand, is widespread. For example, one in five adolescents with ADHD in US has reported of being asked to sell or trade his or her medication at least once during the last five years (Kollins, 2007). Users tend to be Caucasian males, and the prevalent purpose of use is to improve academic performance, more than to "get high" (Bogle & Smith, 2009).

Can drug addicts benefit to some extent from MPH? Drug addiction is commonly associated with cognitive impairments in attention, working memory and response inhibition (see e.g., Lovallo et al., 2006). The extent of these impairments

was found to predict treatment retention and relapse, as well as treatment success. Thus, cognitive enhancement of addicted individuals may ameliorate treatment outcome (Sofuoglu, DeVito, Waters, & Carroll, 2013). Several investigations suggest that MPH can produce cognitive enhancement among substance users: in an fMRI study of cocaine users, a single dose of 20 mg MPH normalized hypoactivation in the anterior cingulate cortex, a region in the prefrontal cortex involved in conflict resolution, and generally a part of the executive control system. It also improved response inhibition (Goldstein et al., 2010). In another study of cocaine abusers, intravenous MPH improved response inhibition compared to placebo (Li et al., 2010).

Finally, several studies have investigated whether MPH and other stimulants taken as part of a treatment program can reduce cocaine use. The results of a recent meta-analysis (Castells et al., 2010) showed that stimulants improved sustained cocaine abstinence (though they ha not effect on retention in treatment). Still, the trend was only significant for bupropion, dextroamphetamine, and modafinil and not for MPH. MPH was found, however, to reduce cocaine use among cocaine users with comorbid ADHD (Levin, Evans, Brooks, & Garawi, 2007). Thus, at present, it appears that MPH may enhance certain cognitive capabilities, but these are not typically manifested in reduced drug abuse, unless the person also has ADHD.

Mini-Dictionary of terms

Abuse liability: The extent to which a substance can lead the user to dependence or abuse of it.

Attention Deficit/ Hyperactivity Disorder (ADHD): A developmental disorder which can persist into adolescence and adulthood. Its core symptoms are inattention and hyperactivity/ impulsivity.

Comission error: Failure to withhold response for a stimulus that does not require responding (e.g., in a Go/No-Go task).

Digit span test (forwards and backwards): One of the many tasks designed to measure verbal working memory; requires holding new information in mind and manipulating it.

Go/No-Go Task: A computerized task intended to measure response inhibition. The participant is presented with letters which appear on the screen one at a time, and is asked to press a button in response to certain letters and withhold response when other letters appear.

Iowa Gambling task: A task intended to measure the ability to make decisions weighing in past information in order to enhance future outcomes; performance was found to involve multifaceted capacities.

Omission error: Failure to respond to a stimulus that requires responding (e.g., in a Go/No-Go task).

Multiple Analysis of Variance (MANOVA): An analysis of variance (ANOVA) involving multiple dependent measures.

Response inhibition: The ability to withhold a prepotent response. This includes the ability to suppress an automatic response, and to change an ongoing response pattern as the demands of the situation change.

Sustained attention: The ability to stay focused on a task and to maintain one's performance level over time, specifically when the task is monotonous and unrewarding, and requires passively attending to it.

Test of Variables of Attention (TOVA): One of the many continuous performance tests (CPTs), which are rapid Go/No-Go tasks in which participants have to discriminate predetermined target stimuli from distracting non-targets.

Two-by-two research design: A research manipulation involving two independent variables, each with two levels (e.g., placebo/Ritalin, healthy adults/individuals with ADHD), in a given sample.

Working memory: The cognitive and neural component responsible for holding current information in mind and manipulating it, while linking it with long-term memory storage. It includes verbal and non-verbal processes (e.g. visual imagery).

Key facts of Methylphenidate

- Methylphenidate (MPH) is the active ingredient of stimulant drugs such as ritalin and concerta that are frequently prescribed to individuals with Attention Deficit / Hyperactivity Disorder (ADHD).
- MPH is different from other stimulants in that there is a substantial period of time (up to an hour) between its consumption and its effects.
- MPH has several physiological side effects, the primary one being fast, pounding, or uneven heartbeats. Headaches, stomachaches, and lack of appetite have also been reported.
- While commonly prescribed for ADHD, MPH is increasingly used by healthy adults (e.g., 12.4% of Nature survey responders).
- The widely held clinician belief that MPH has a negative effect on cognitive functioning in individuals without ADHD is not consistent with the empirical evidence, which shows marked improvement in various aspects of cognitive functioning for individuals without ADHD.

Key facts of ADHD

- Attention Deficit/ Hyperactivity Disorder (ADHD) is a developmental disorder which can persist into adolescence and adulthood. Its core symptoms are inattention - a difficulty to sustain attention and to ignore distractions, and hyperactivity/impulsivity - a difficulty to self-regulate one' actions according to the situation demands.
- According to DSM-5, the prevalence of ADHD is estimated to be 5% among children, and 2.5% among adults. Boys are more likely to have ADHD than girls, the ratio being 2:1 among children and 1.6:1 among adults.
- The causes for ADHD have been explained by neurological, genetic, cognitive, environmental, and cultural models. It is highly inheritable, but genetics explains only about 50% of the variance. The other 50% are yet to be elucidated by future research.
- ADHD can have significant implications in various life settings: at school these individuals can be underachievers despite intact or even high IQ, due to their performance deficits; the behaviors characterizing these individuals can result in problems with their peers, their teachers, and their parents. Adults with undiagnosed or untreated ADHD can suffer educational, occupational, interpersonal, and emotional problems.
- Stimulant medications are commonly prescribed for ADHD treatment. About 20% do not respond to stimulant treatment, and are treated with anti-depressants instead. In addition, psychosocial interventions are highly recommended in order to fully treat this multifaceted disorder and its implications.

Summary points

- The reviewed findings suggest that MPH effectively enhances sustained attention, response inhibition, and working memory capacities; yet not only for individuals with ADHD, but also for those without ADHD.
- Individuals who seem most affected by MPH are those with a profile of low task performance in the given task.
- The effect of MPH occurs most strongly under challenging task conditions.
- The findings concerning the long term effect of MPH are less conclusive, yet there is no evidence of considerable physical harm or risk of subsequent abuse as long as dosage remains low.
- The beneficial effects of taking MPH seem to be limited to the treatment period; there is no definite evidence for accumulated effects.

Figure Titles

Figure 1: A: Illustration of stimuli from the Test of Variables of Attention (TOVA). B: Shalev et al.'s (2012) study results in medical students.

Figure 2: A: TOVA overall scores in Agay et al. (2010). B: Response-sensitivity scores in Agay et al. (2010).

Figure 3: A scatter plot of performance change with MPH in the Test of Variables of Attention (TOVA) as a function of baseline performance in Agay et al. (2014).

Figure 4: A scatter plot of performance change with MPH in the Iowa Gambling Task (IGT) as a function of baseline performance in Agay et al. (2014).

Figure 5: A hypothetical distribution demonstrating demographical conditions giving rise to confounding between functional aspects (high/low performance) and diagnosis for a target population.

Figure Legends

Figure 1: A: The two first blocks of the task had a 1:3.5 Target to Non-target presentation rate, while the two following blocks had a 3.5:1 Target to Non-target rate. B: The rate of omission and commission errors (in percents) in the placebo and MPH conditions administered within subjects, in two order controlled sessions, in Shalev et al. (2012). Error terms denote the standard error of the mean (based on reported standard deviations).

Figure 2: The error terms denote standard errors.

Figure 5: Because in this illustration the target population under-performs compared to the healthy adult population, effects of treatment on low performing individuals may be confounded with the diagnosis for the target population.

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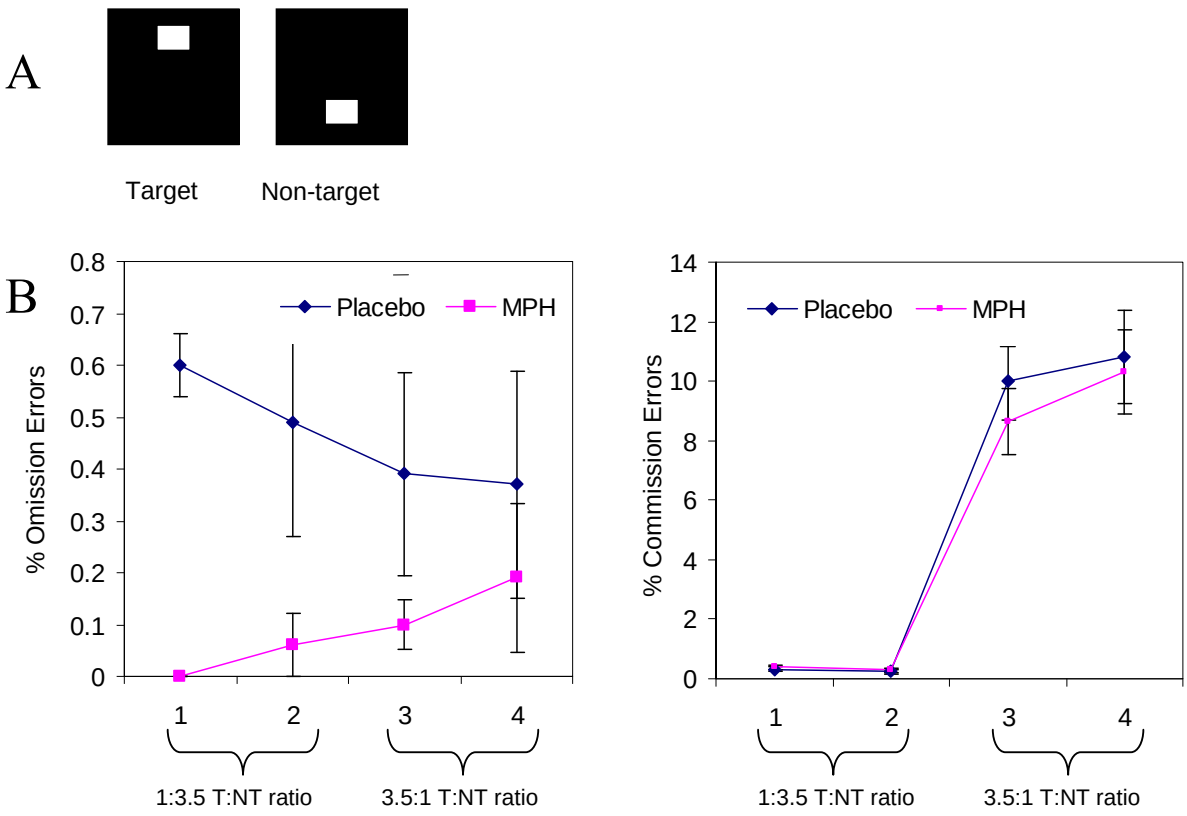
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3.5:1 T:NT ratio
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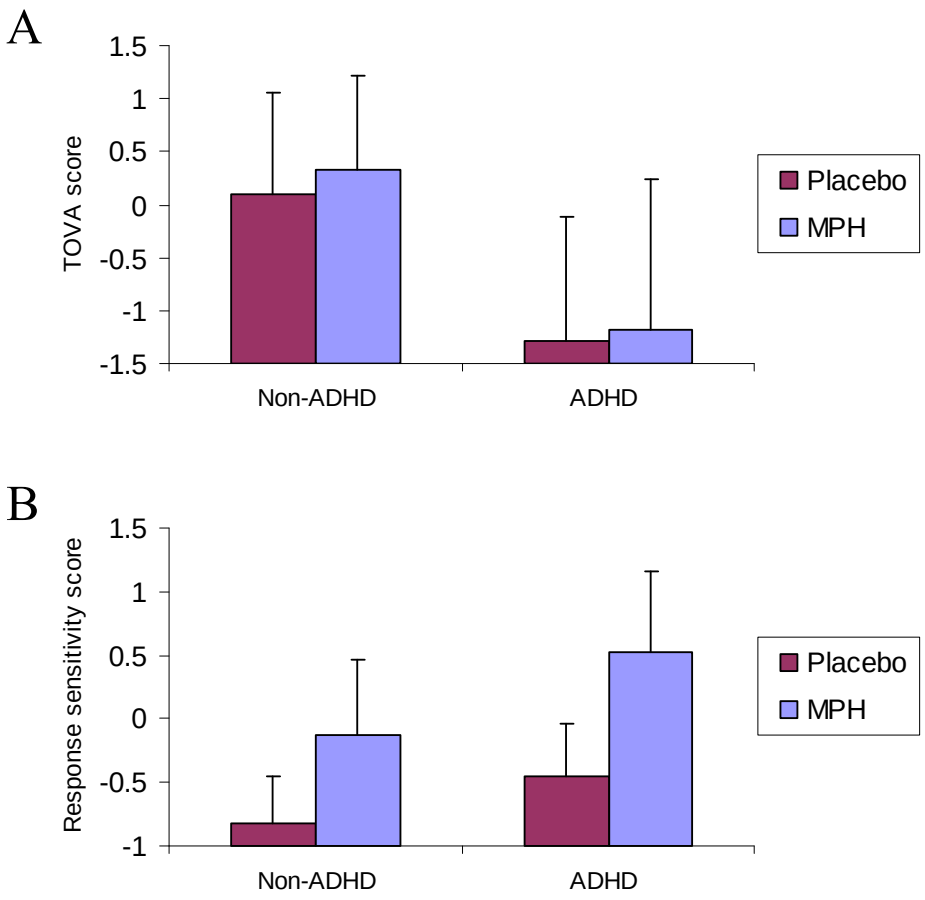
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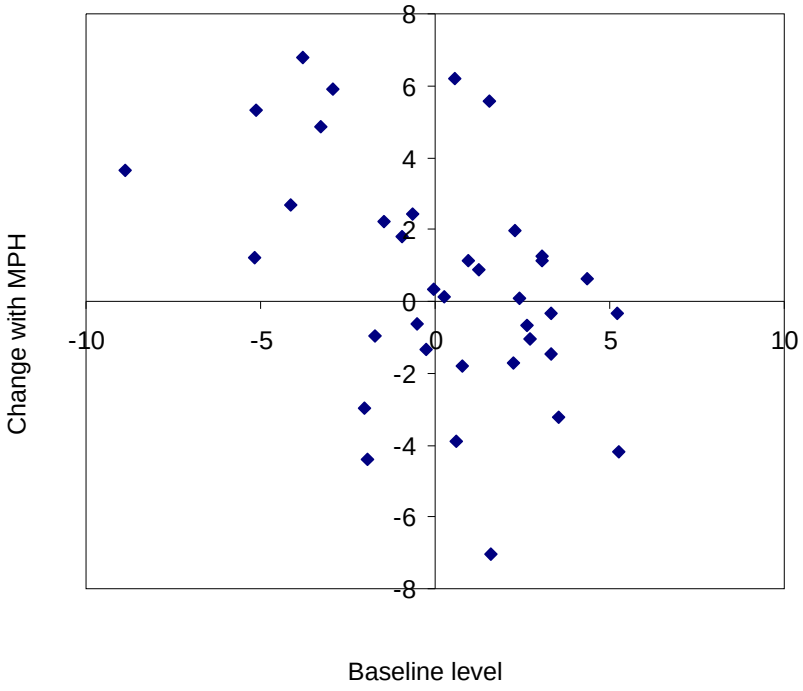

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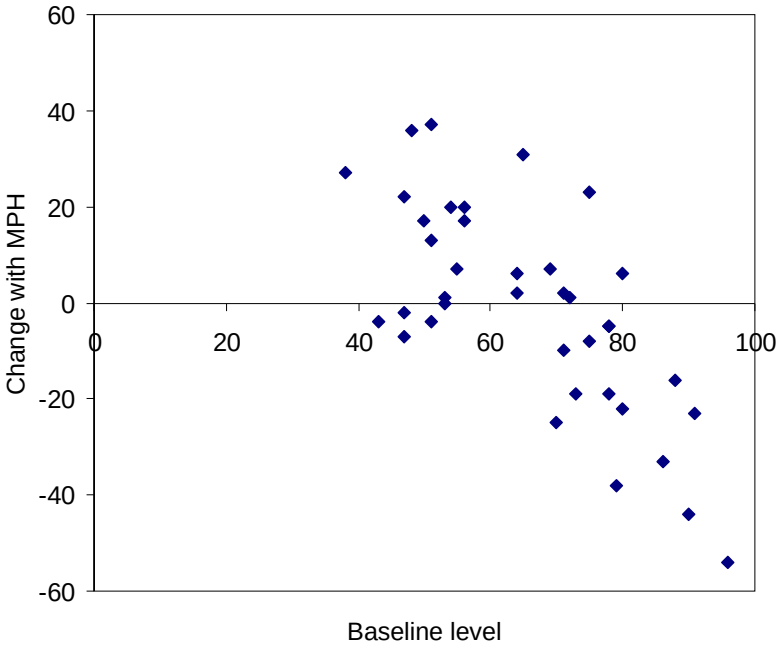
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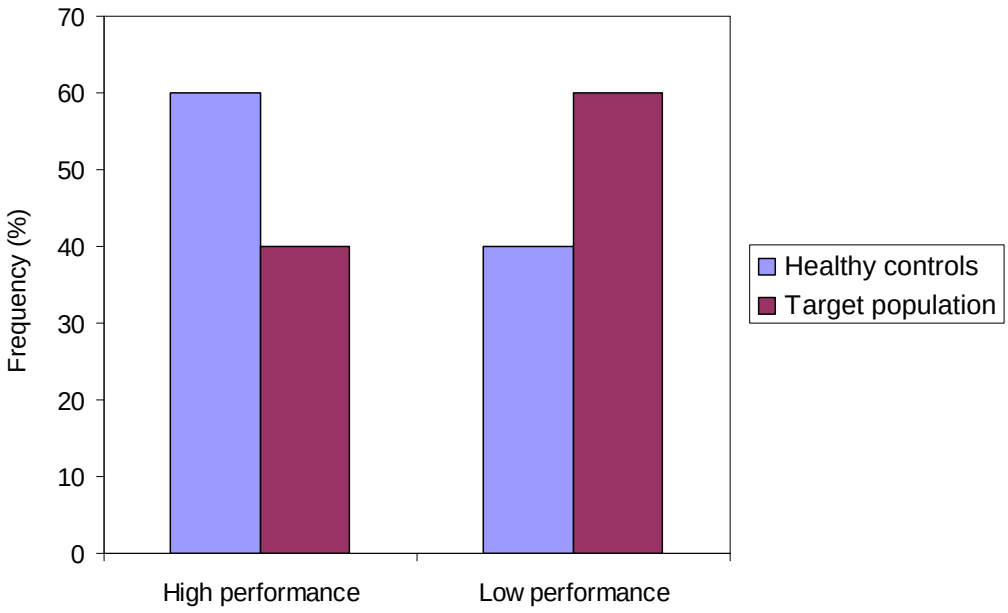
Change with MPH
Baseline level

Figure 5: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Frequency (%)
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Healthy controls
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