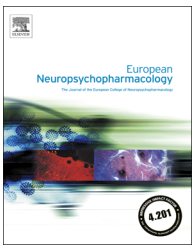
European Neuropsychopharmacology (2014) 24, 200–206



www.elsevier.com/locate/euroneuro

Cognitive effects of methylphenidate and levodopa in healthy volunteers

A.M.W. Linssen*, A. Sambeth, E.F.P.M. Vuurman, W.J. Riedel

Department of Neuropsychology and Psychopharmacology, Faculty of Psychology and Neuroscience, Maastricht University, PO Box 616, 6200 MD, Maastricht, The Netherlands

Received 29 January 2013; received in revised form 16 September 2013; accepted 26 September 2013

KEYWORDS
Memory;
Event-related potentials;
Dopamine;
Methylphenidate;
Levodopa

Abstract
Our previous study showed enhanced declarative memory consolidation after acute methylphenidate (MPH) administration. The primary aim of the current study was to investigate the duration of this effect. Secondary, the dopaminergic contribution of MPH effects, the electrophysiological correlates of declarative memory, and the specificity of memory enhancing effects of MPH to declarative memory were assessed. Effects of 40 mg of MPH on memory performance were compared to 100 mg of levodopa (LEV) in a placebo-controlled crossover study with 30 healthy volunteers. Memory performance testing included a word learning test, the Sternberg memory scanning task, a paired associates learning task, and a spatial working memory task. During the word learning test, event-related brain potentials (ERPs) were measured. MPH failed to enhance retention of words at a 30 min delay, but it improved 24 h delayed memory recall relative to PLA and LEV. Furthermore, during encoding, the P3b and P600 ERP latencies were prolonged and the P600 amplitude was larger after LEV compared to PLA and MPH. MPH speeded response times on the Sternberg Memory Scanning task and improved performance on the Paired Associates Learning task, relative to LEV, but not PLA. Performance on the Spatial working memory task was not affected by the treatments. These findings suggest that MPH and LEV might have opposite effects on memory

1. Introduction

Methylphenidate (MPH) has been shown to not only reduce behavioral symptoms of children with ADHD, but also improve cognitive function in this group (Pietrzak et al., 2006). Some cognition enhancing effects have also been demonstrated in healthy volunteers (Repantis et al., 2010; Smith and Farah, 2011). MPH enhances performance in normal controls most notably on tasks measuring speed of processing or working memory (Agay et al., 2010; Elliott et al., 1997; Kollins et al., 1998; Linssen et al., 2011; Mehta et al., 2000). However, a recent study showed that MPH also improves declarative memory consolidation in healthy individuals (Linssen et al., 2012). It showed enhanced memory recall for words, 30 min after word list learning if the lists were studied under the influence of MPH. So far, it is still unknown how long this effect lasts. The memory consolidation effect of the pharmacologically similar drug amphetamine has been shown

*Corresponding author. Tel.: +31 433881757; fax: +31 433884560.
E-mail address: amw.linssen@alumni.maastrichtuniversity.nl (A.M.W. Linssen).

0924-977X/$ - see front matter © 2014 Elsevier B.V. and ECNP. All rights reserved.
http://dx.doi.org/10.1016/j.euroneuro.2013.09.009

to still be present after a 24 h delay (Zeeuws and Soetens, 2007), indicating a role in late consolidation processes. In the present study, our primary aim was therefore to investigate if the effect of MPH on memory consolidation is also still present a day after word learning.

MPH blocks the reuptake of the catecholamines dopamine and noradrenaline by binding to the transporters, thereby increasing catecholamine availability (Hannestad et al., 2010; Kuczenski and Segal, 1997; Volkow et al., 1998). It is suggested that MPH's potency may be higher for the noradrenaline- than the dopamine transporter (Kuczenski and Segal, 1997), but as dopamine is also transported by the noradrenaline transporter, it is not clear which neurotransmitter system is more affected by MPH (Hannestad et al., 2010; Pacholczyk et al., 1991). Both modulation of noradrenaline- and dopamine alters cognitive function (Chamberlain et al., 2006; Nieoullon, 2002) and hence, MPH's effect on memory consolidation may be mediated through either dopamine, noradrenaline or both. It is difficult to study dopamine and noradrenaline in isolation as catecholamine-transporter blockers, even if specifically blocking only one transporter type, will affect both neurotransmitters and dopamine is a precursor of noradrenaline. However, by comparing MPH to levodopa (LEV), the precursor of dopamine and a predominantly dopaminergic drug, dopaminergic effects could be largely disentangled from noradrenergic effects (Breitenstein et al., 2006).

A secondary aim of the present study was to study the dopaminergic contribution to MPH's effects on memory by comparing effects of LEV to those of MPH on memory in healthy volunteers. Furthermore, we investigated if behavioral results are also reflected by electrophysiological changes in the brain. The present study therefore included electro-encephalography (EEG) measurements, from which event-related potentials (ERPs) were extracted. A previous study showed that a visual word learning task as used in the present study elicits a specific waveform showing several relevant ERP components, including for example P3a and P3b (Linssen et al., 2011). However, because little is known about the effects of dopaminergic manipulation on ERP components measured during a word learning task we chose an exploratory approach. The ERPs were extracted and inspected for the presence of different ERP components, without making specific a priori hypotheses about changes in amplitude and latency of the various components. Finally, to study the specificity of MPH for declarative memory, several other memory tasks, including spatial and verbal (working) memory tasks, were administered.

To address these aims, the effects of a 40 mg dose of MPH on behavioral and electrophysiological measures of a visual word learning task and several other memory tasks were compared to the effect of 100 mg of LEV in a placebo controlled crossover designed study with 30 healthy volunteers. Heart rate, blood pressure and subjective measures were included as control measures.

2. Experimental procedures

2.1. Participants

Thirty-two healthy volunteers were included, thirty of which completed the study (20 male, 10 female, mean age=20.7, SD=2.3, range=18–28). The two participants who dropped out canceled their participation because of other obligations. Participants were recruited by means of local advertisements and were paid to participate. Prescreening occurred using a medical history questionnaire and was followed by medical examination.

The main inclusion criteria were: between 18 and 45 years of age, body mass index between 18 and 30 kg/m^2, normal binocular activity (corrected or uncorrected). The main exclusion criteria were history or presence of mental or physical disorders, consumption of more than 21 alcohol units per week or more than five caffeine-containing drinks per day, pregnancy or lactation, use of medication other than oral contraceptives, use of recreational drugs from 2 weeks before until the end of the experiment.

All subjects gave written informed consent. The study was carried out in accordance with the Declaration of Helsinki (WMO, 2008) and approved by the medical ethical committee of Maastricht University.

2.2. Design

The study was conducted according to a double-blind, placebo-controlled, three-way crossover design. Between the testing days, a period of at least 48 h elapsed, but generally, testing days were scheduled approximately one week apart. Each participant received one of three single treatments including placebo (PLA), 40 mg of MPH and 125 mg of levodopa/carbidopa (LEV) on each testing day (see Supplementary material). LEV was given in combination with 10 mg of domperidone (a peripheral dopamine antagonist) to prevent nausea.

2.3. Dependent measures

See Supplementary material.

2.3.1. Visual verbal learning test

The visual verbal learning test (VVLT) was used to measure declarative memory (Klaassen et al., 2002). This task is an adapted version of Rey's Auditory Verbal Learning Test (Lezak, 1995) using lists of 30 monosyllabic words in Dutch, validated by Klaassen et al. (2002) and used in multiple published experiments since (e.g. (Linssen et al., 2012; Sambeth et al., 2007; van Ruitenbeek et al., 2008)). The presentation of the same 30-word list was repeated three times in total using the same sequence of words, each time followed by immediate free verbal recall of all remembered words, which is recorded by the experiment leader. Thirty minutes after immediate free recall of the final series, participants were subjected to a delayed verbal recall test and a forced-choice recognition test. Twenty-four hours later participants were again subjected to a delayed verbal recall and recognition test (using a different set of new words). Three parallel lists were used, using a different list for each of the three testing days. Sequence of the lists was balanced across testing days (see Supplementary material).

During the visual verbal learning task, EEG was recorded using 3 electrodes attached to a cap according to the international 10–20 system (Jasper, 1958) at the Fz, Cz and Pz electrode positions (see Supplementary material).

In the ERPs extracted from the electroencephalogram during encoding several peaks could be discerned. P3a and P3b are two subcomponents of the P300, which is interpreted as reflecting brain activity related to updating the mental representation of incoming stimuli (Polich, 2007; Polich and Criado, 2006). P3a is induced by novel or unexpected stimuli, while P3b is associated with context updating and subsequent memory storage (Coull, 1998; Polich, 2007). P600, sometimes referred to as late positive component or positive slow wave has been associated with several higher-level functions, including syntactic processing, item recognition and working