Effect of an acute d-amphetamine administration on context information memory in healthy volunteers: evidence from a source memory task

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Rationale  Previous research demonstrated a positive effect of d-amphetamine on long-term verbal memory. An improvement in memory for contextual information is proposed as a possible mechanism underlying the d-amphetamine facilitation effect.

Objectives  A double blind, placebo controlled experiment was used to examine the processes involved in episodic memory affected by an acute administration of d-amphetamine. We investigated whether positive effects of d-amphetamine on item memory could be extended to context information by using a source memory paradigm.

Methods  In a within-subjects design with two sessions, two study lists were presented in each session and participants were required to make an old/new recognition decision (item memory) and a list discrimination judgement (source memory) after delays of 1 h, 1 day and 1 week.

Results  Enhancement of item memory after d-amphetamine intake was observed on delayed tests only, confirming that amphetamine does not affect short-term memory or memory acquisition, but rather a process operating after initial encoding. Importantly, we found an enhancement in remembering the source of recognized items after d-amphetamine administration.

Conclusion  The present study suggests that an acute administration of d-amphetamine helps to bind different features of an item in memory, in turn leading to an increased ability to recollect both the item and its context. Copyright © 2010 John Wiley & Sons, Ltd.

Key words— d-amphetamine; human memory; consolidation; context information

INTRODUCTION

The way information is stored in memory for long-term use is still one of the most fascinating issues in human memory. Memory consolidation, a post-encoding process by which new memories become more permanent and resistant to disruption, is an engaging idea that originated more than a century ago in Müller and Pilzecker’s work on retroactive inhibition (Lechner et al., 1999; McGaugh, 2000). Traditionally, ‘consolidation’ refers to the idea that long-term memory storage develops gradually after learning. Despite more than a century of theorizing, the exact nature of the consolidation process is still unclear, and the idea of consolidation remains controversial (e.g. Meeter and Murre, 2004; Moskovitch and Nadal, 1998). Although there has been an upsurge of interest since 2000 (e.g. Brown, 2002; Dudai and Morris, 2000; Haist et al., 2001; McGaugh, 2000), consolidation research in humans remains scarce and the majority of studies have been conducted with animals.

Animal studies show that memory traces remain vulnerable to modulation shortly after learning (e.g. Doty and Doty, 1966; Krivanek and McGaugh, 1969; McGaugh and Herz, 1972). For instance, a facilitating effect of central nervous system (CNS) stimulants, such as amphetamines, on long-term memory storage has been demonstrated on a variety of tasks (Brown et al., 2000; Krivanek and McGaugh, 1969). Amphetamine, a sympathomimetic amine with CNS stimulant properties, acts as a substrate for norepinephrine, serotonin and dopamine transporters, and induces the release of these neurotransmitters into nerve synapses, hereby promoting nerve input transmission (Rothman et al., 2001). Recent studies seem to indicate that it is the increase of norepinephrine levels in the amygdala, hippocampus and cortex that is associated with memory enhancement (LaLumiere et al., 2003; Tzavara et al., 2006; Wiig et al., 2009).

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Studies on humans showed an improvement of episodic memory with verbal material after an acute administration of d-amphetamine (Breitenstein et al., 2004; Brown et al., 2000; Rapoport et al., 1980; Soetens et al., 1995; Weingartner et al., 1982; Zeeuws and Soetens, 2007). There is growing evidence that the d-amphetamine facilitation demonstrated in verbal memory arises from a specific modulation of the consolidation process, rather than affecting encoding or retrieval processes (Breitenstein et al., 2004; Soetens et al., 1995; Zeeuws and Soetens, 2007). This can be inferred from the observation that d-amphetamine improves delayed recall only and that the enhancement is also found when the drug is administered after learning (McGaugh, 2000).

Importantly, the time course of the drug effect seems to depend highly on the type of memory task. As shown by Soetens et al. (1995), the d-amphetamine facilitation effect in recall emerged already 1 h after list learning, whereas with recognition tests there was a tendency towards memory improvement after one-day delay (DD), with the effect only reaching significance after 1 week. A possible explanation for the late emergence of d-amphetamine advantage in recognition relative to recall tasks is that recognition tasks are easier and that complex or demanding tasks are more susceptible to drug effects than simple tasks. For example, research with benzodiazepines showed that free recall tasks are more sensitive to subtle drug effects than relatively easier cued recall and recognition tasks (Curran, 2000). However, pilot studies in our lab showed that performance level decreased significantly when abstract words were used, yet the time course of the drug effect was unaffected.

A more probable explanation for the difference in time course of the drug effect between recall and recognition tasks is the amount of context information. Storage of contextual information surrounding an event allows the event to be encoded in memory as a unique trace that can be distinguished from other similar events (Tulving and Thomson, 1973). Context information could be any extra information about an item, such as time or location of presentation during encoding. Especially relevant for the current study is that recall performance is known to be more context-dependent than recognition (see e.g. Smith, 1988 for a review). This begs the question how much of the memory improvement under influence of d-amphetamine can be ascribed to the enhancement of contextual retrieval.

In the present study we examined the influence of d-amphetamine on contextual information by using a source memory paradigm (e.g. Johnson et al., 1993) in a recognition task. In a typical source memory paradigm, participants are presented with stimuli in two different contexts (e.g. time of learning) during an initial learning phase. After a delay, they are tested on their memory both for the stimuli (item information) and for the context in which the stimuli were presented (source memory). Source memory includes the recollection of the spatiotemporal circumstances and physical features of stimulus presentation, as well as memory for the cognitive operations and emotional states during stimulus perception (Johnson, 2005; Johnson and Raye, 2000). Binding such features of an event and maintaining these connections could be an essential component of episodic memories. In most episodic tasks, the items being learned are already familiar to the participants, but they have to be remembered in the context of the task. Therefore, when an item is perceived during a study event, a binding node is primed to form connections between the episodic context and the meaning of the items (e.g. words). Participants thus need to attach some kind of tag or other indicator during encoding, so that they can determine that the item was presented during that particular study phase. In the current study, as in most similar studies, we measured context information by testing only one aspect of source memory. Since memory questions, especially in episodic memory, often require a person to recall when something happened, we tested the temporal aspect of context information.

In the present study, we administered 10 mg d-amphetamine orally, 60–90 min before the study phase. Although we cannot exclude that the administration of the drug at another point in time, or with another dose may result in a different pattern of memory improvement, the present design can be justified on the basis of the planned target issue. Therefore, we replicated the design of an earlier study (Soetens et al., 1995) where we found a positive effect of d-amphetamine after 1 week in a recognition experiment, using the same drug dose, in order to make a better comparison across studies. The only difference with that study is that participants were now supplementary asked for the source of the recognized items. The main issue of the present study was to find out whether the memory improvement with d-amphetamine could be related to an improvement of context memory.

In sum, the purpose of this study was to examine whether context information is positively affected by d-amphetamine in the same way as item memory. Such an effect can possibly explain the differential time course of the drug effect in recall and recognition. Participants studied two lists of words and were subsequently asked to make an old/new recognition
decision (item memory) and a list discrimination judgement (source memory) on different test moments. In agreement with previous studies (Soetens et al., 1993; Soetens et al., 1995; Zeeuws and Soetens, 2007), we predicted that the d-amphetamine facilitation effect would only emerge on delayed item recognition tests, more specifically after one-week delay (WD). More importantly, we assumed that, if d-amphetamine improves episodic memory through the binding of context features, a positive effect should emerge on context information.

METHOD

Participants

Participants were 17 male paid volunteers, between the ages of 18 and 30 ($M = 21.56; \text{SD} = \pm 2.39$). They were recruited via advertisement in the university newspaper. All signed an informed consent prior to participating. Participants were excluded if they were currently using any type of medication, if they had a history of drug abuse, or if they had a physical or mental illness. All participants were unaware of the nature of the administered drug. None of them had previously participated in similar experiments. The Ethical Commission of the Faculty of Medicine of the Vrije Universiteit Brussel approved of the experimental design.

Materials

Drug. Drug dose was established at 10 mg d-amphetamine. This dose is comparable to the average daily starting dose of amphetamine administered to ADHD patients. Identical and unmarked capsules of drug and placebo were administered orally 1 h before the study phase. Pharmacokinetic data indicate that plasma levels of orally administered d-amphetamine peak 1.5–3 h after administration, cardiovascular effects occur at 60–120 min and behavioural effects peak 120 min after d-amphetamine intake (Angrist et al., 1987; Fabian and Silverstone, 1997).

Word lists. Eight lists of 70 unrelated Dutch words were composed. Each word consisted of 3–7 letters and one syllable. For each participant two of the eight lists were chosen randomly as target lists in each study session (List 1 and List 2), and the words of two other lists were used as distractors during the recognition tests. The lists were counterbalanced across subjects and sessions as much as possible, following a Latin Square design. The words in each list were matched in frequency according to the norms provided by Uit den Boogaart (1975).

To exclude primacy and recency effects, the first 5 and last 5 words from each list were not tested. Consequently, 60 target items of List 1 and 60 target items of List 2 were used on subsequent recognition tests. The 60 target words of each list were spread across 4 recognition tests, so that 15 words of List 1 and 15 words of List 2 were presented on each test. On each recognition test, a 60-word sequence was presented, comprising these 30 studied items and 30 distractors. Different target and distractor words were used on each recognition test, so that each item was tested only once. Test items were presented in a random order in the centre of the screen. Responses were made with the 1 and 3 keys of the numerical keyboard, using index and middle finger of the right hand. The experiment was run on IBM compatible Pentium 4 computers with 17-inch screen, using E-Prime Version 1.1 Service Pack 3 software (Schneider et al., 2002).

Subjective state tests. The Profile of Mood State (POMS) and the Activation–Deactivation Adjective CheckList (AD-ACL) were administered at different moments (see Procedure). The POMS consist of the following variables: tension, depression, anger, fatigue and vigor (Wald and Mellenbergh, 1990). The AD-ACL contains following variables: general activation, general deactivation, sleepiness and tension (Kerkhof, 1998).

Procedure

We used a double blind, crossover, placebo-controlled, $2 \times 4$ factorial design with drug treatment (d-amphetamine and placebo) and test moment (immediate, one-hour delay (HD), DD and WD) manipulated within-subjects. Sessions were separated by a one-week washout period (see Figure 1). To ensure minimization of order effects of drug administration and lists, both factors were counterbalanced across subjects and sessions. The participants were tested individually in semi-darkened cubicles at the Psychological Laboratory of the Vrije Universiteit Brussel. All sessions began at the same time in the morning. The study phase was conducted between 60 and 90 min after the oral administration of 10 mg d-amphetamine or placebo. Although the behavioural effect of amphetamine is assumed to peak at a later moment (120 min), we preferred to use the same intervals as in previous studies to avoid the introduction of extra variability in comparing across studies. Participants remained in the laboratory
between the time of administration and the start of the study phase.

Study phase. In each study-session, participants had to study 2 lists of 70 words each. Just prior to list presentation, participants were informed that they would see a series of words and that they should try to remember the words for a later (unspecified) memory test. Following instructions, the words were presented in the centre of the screen in lower case at a constant rate of 2 s per word with an interstimulus interval (ISI) of 250 ms. After the items of List 1 were displayed, there was a 30-min break followed by the presentation of List 2. The length of the break was based on the results of pilot studies, which showed that shorter breaks lead to source memory scores, close to chance level (0.50). During the break participants performed a non-verbal distractor task.

Testing phase. After the presentation of the words of List 2, the item recognition test started (immediate recognition, Imm). This involved the presentation of a 60-word sequence comprising a random combination of 30 studied items and 30 distractors, with 15 target items from List 1 and 15 targets from List 2. The test phase was self-paced and test items were presented in the centre of the screen. Each item was accompanied by a label at the bottom of the screen, instructing the participants to indicate whether they recognized the word as being presented during the study phase by pressing one of the two response keys (press ‘1’ if they recognized the word and press ‘3’ if they thought it was a new word). After a response, there was a 250-ms ISI, followed by the presentation of the next test word. The immediate recognition test was then followed by a non-verbal distractor task, which lasted approximately 50 min (see Figure 1 for a summary of the experimental procedure).

HD, DD and WD after list learning, participants were again asked to do an old/new recognition test. Again, the recognition tests consisted of 30 studied items, half coming from List 1 and the other half from List 2, and 30 distractor items. If the answer was ‘new’, the next test item was shown. However, unlike the immediate recognition test, after an ‘old’ response, the instruction ‘In which list have you seen this word?’ was displayed on the screen. Participants had to press ‘1’ if they thought the recognized word was coming from List 1 and press ‘3’ if they thought it was coming from List 2. After participants made the source judgement, the next test item was presented. No feedback was provided during any of the testing phases.

In order to assess whether d-amphetamine-induced mood changes could be responsible for any improved memory performance, the subjective state of the participants was recorded. All participants completed the POMS and the AD-ACL on each session before drug administration (baseline), approximately 2 h after administration, and after 1 day. Debriefing followed after the last session.
RESULTS

A $2 \times 4$ repeated measures ANOVA was conducted on the corrected item recognition scores, sensitivity ($d'$) and response bias (C) for item information with drug treatment (d-amphetamine and placebo) and test moment (Imm, HD, DD and WD) as within-subject factors. Since context information was not tested on the immediate test moment, a separate $2 \times 3$ repeated measures ANOVA with drug treatment (d-amphetamine and placebo) and test moment (HD, DD and WD) as within-subject factors was conducted on the source memory scores. Because a significant d-amphetamine facilitation effect was only expected at the WD test and no drug effect was expected at earlier test moments, the data were further analysed with LSD planned comparisons with Bonferonni correction (Anderson, 2001).

All analyses were first done taking into account the factor ‘order of drug treatment’. As no main effect or interaction effects were found in relation with this factor, we removed it from all analyses.

Corrected item recognition memory

Corrected item recognition scores were computed as the proportion of hits, regardless of source accuracy, minus the proportion of false alarms (e.g. Foley et al., 1983; Johnson et al., 1996; Mintzer and Griffiths, 1999; Murnane and Bayen, 1996). See Figure 2 for an overview of the corrected item information.

The ANOVA on item recognition scores revealed a significant drug effect [$F(1,16) = 11.31; p < 0.01$], with a higher amount of correctly recognized items in the d-amphetamine condition as compared to the placebo condition. As expected, a main effect of test moment was observed, showing memory performance dropped over time [$F(3,48) = 203.88; p < 0.001$]. However, no interaction was found between drug treatment and test moment [$F(3,48) = 0.55; \text{ns}$]. This was expected, since we only predicted an effect of d-amphetamine after one-week delay (Soetens et al., 1995). Since a priori hypotheses were formulated concerning the precise timing of the drug effect, the main effect of drug was further analysed with LSD comparisons with a Bonferonni correction (Anderson, 2001). In line with previous studies, no d-amphetamine facilitation effect was observed on the immediate and the HD test (all $p > 0.30$). A tendency towards significance was observed at the DD test ($p < 0.10$) and as expected, a significant drug effect on item recognition memory only emerged after WD with a higher proportion of hit rates with d-amphetamine relative to placebo ($p < 0.05$).

Sensitivity $d'$ and decision criterion C (see Table 1)

Sensitivity ($d'$) and criterion (C) were calculated according to the signal detection theory (MacMillan and Creelman, 2005). The analysis on $d'$ revealed the same pattern as for corrected item recognition: after d-amphetamine intake there was a significant main effect of drug treatment, [$F(1,16) = 6.03; p < 0.05$], indicating participants were better at discriminating between target and distractors items, a significant drop in sensitivity over time [$F(3,48) = 110.47; p < 0.001$], and no interaction between drug treatment and test moment [$F(3,48) = 0.65; \text{ns}$]. Analyses using LSD comparisons...
with Bonferroni correction showed no effect of d-amphetamine on the immediate, the HD and the DD test \(p > 0.10\). Again, as expected, the drug effect only emerged after WD, showing that participants with d-amphetamine were better able to discriminate between targets and distractors after one-week delay \(p < 0.05\).

The analysis on C revealed no drug effect \(F(1,11) = 0.03; \text{ns}\). A tendency towards more conservative responses when time passed by was observed \(F(1,11) = 3.44; p < 0.10\). There was no interaction between drug and test moment \(F(1,16) = 0.08; \text{ns}\).

Source memory

Source memory scores were calculated by dividing the number of hits attributed to the correct source by the total number of hits (e.g. Foley et al., 1983; Johnson et al., 1996; Mintzer and Griffiths, 1999; Murnane and Bayen, 1996). Analyses on the source memory scores showed a clear d-amphetamine facilitation effect \(F(1,16) = 13.25; p < 0.01\). There was no general drop

Subjective ratings

The changes in memory performance occurred in the absence of any subjective alterations in mood, as measured by the variables of the POMS and the AD-ACL (all comparisons \(p > 0.05\)). The results showed that improved recognition memory was independent of d-amphetamine-induced mood changes.

DISCUSSION

The purpose of the present study was to further unravel the precise nature of the d-amphetamine facilitation effect on human verbal memory. Drug effects on episodic memory for item information and context information were evaluated using a source memory paradigm (e.g. Johnson et al., 1993).

The present findings are in line with previous studies, in that a significant d-amphetamine facilitation effect was found on item recognition memory performance. As expected, there was no effect of the drug on the immediate test moment (Soetens et al., 1995) suggesting that the drug does not directly affect acquisition or
short-term memory. In addition, d-amphetamine facilitation was only observed at delayed tests, providing further support for the conjecture that the drug modulates a process operating after initial encoding (McGaugh and Roozendaal, 2009; Soetens et al., 1995; Zeeuws and Soetens, 2007). An increased level of arousal cannot account for the present d-amphetamine facilitation on memory either, because the positive effect was found at a time that participants were not under influence of the drug. Also, an indirect influence of increased arousal on immediate recognition is improbable. Psychologically, arousal leads to a condition of raised alertness and an increased readiness to respond to stimuli (Dickman, 2002). Translated into the design of the present study, an increased readiness to respond should be accompanied by an increase in false alarms in immediate recognition. Like in previous studies, the rate of false alarms was not influenced by d-amphetamine (Kelly et al., 1991; Koelega, 1993; Soetens et al., 1995). The conclusion that memory enhancement with d-amphetamine cannot be ascribed to an increase in the level of arousal has further been corroborated by animal studies with l-amphetamine, an amphetamine derivate retaining the cognitive enhancing effect of d-amphetamine, but without producing the stimulatory effects. With this derivate Wiig et al. (2009) found an enhanced memory in rats, without measuring an increase in motor activity. Finally, as in other studies, the memory improvements in the present study occurred in the absence of any subjective changes (Soetens et al., 1995; Strakowski et al., 2001; Ward et al., 1997).

Although no empirical test in humans exists which directly examines the consolidation process, the present findings indirectly add further support to the idea of a modulation of the consolidation process to account for the d-amphetamine facilitation effect on item memory (Soetens et al., 1995; Zeeuws and Soetens, 2007). Crucially, the data further showed an enhancement in the memory of temporal information as a consequence of the acute administration of d-amphetamine. This finding is important, because it suggests that d-amphetamine not only increases the likelihood that an item will be remembered/recognized, but that it also increases the ability to recollect contextual details about the study event. Interestingly, the improvement of temporal information with d-amphetamine follows the same time course as the improvement of item recognition. This suggests that both effects are linked to each other.

A possible explanation is that item memory improvement with amphetamine is a consequence of cohesion, a process that is assumed to occur during an early stage of consolidation, and that serves ‘to bind or glue aspects of incoming information into separately retrievable engrams’ (Kroll et al., 1996; Moskovich and Nadal, 1998). Although the exact nature of cohesion is not yet fully understood it is claimed that this process determines the strength of a memory trace. Possibly d-amphetamine enhances this early stage of memory consolidation by specifically modulating the process that contributes to the binding of different features of an episode. A popular hypothesis is that features are bound via synchronized firing of different neurons in the cortex (Axmacher et al., 2006). However, a strengthening of early binding processes cannot explain that memory improvement also occurred when d-amphetamine was administered after learning (McGaugh, 2000; Soetens et al., 1995), and that the effect only emerged after a delay. These results suggest that the drug also influences later stages of the consolidation process. It is possible that the binding of features, as part of the consolidation process, occurred gradually and that a threshold has to be crossed before the effect becomes visible in the recognition data. For example, it could be that there needs to be a minimum time of co-activation of the to-be-remembered item and the context features for building a strong episodic memory trace, and this co-activation could have been prolonged by d-amphetamine. Alternatively, d-amphetamine may act upon later stages of the consolidation process, which are not directly related to cohesion, but which may strengthen recently developed episodic memories. Anyhow, developing and maintaining the connections between features of an event are important aspects of episodic memories. D-amphetamine may promote or maintain feature binding in memory, resulting in more detailed memories that are easier to remember at a later stage.

Enhancement of the memory for temporal information may also provide an explanation for the differential time course of the drug effect in recall and recognition tasks found in previous studies (Soetens et al., 1993; Soetens et al., 1995; Zeeuws and Soetens, 2007). D-amphetamine facilitation occurred 1 h after learning in free recall, but the effect only emerged after 1 week in recognition (Soetens et al., 1995). Recall performance is known to be more affected by context-dependency than recognition performance (see Smith, 1988 for a review), because recall of a specific episode is largely based on the association of the to-be-recalled items with context information. The facilitative effect of d-amphetamine on source memory found in the present study could therefore provide an explanation for the stronger d-amphetamine facilitation effect in recall relative to recognition, causing a different time
course effect of d-amphetamine. However, because the evidence is only indirect, this claim must be considered with caution.

It is important to note that in the current study the drug facilitation effect on source memory was only observed after WD, although this task entailed a recall process. This effect is in contrast with the positive effect of d-amphetamine after 1 h in free recall tasks in earlier studies. However, there is more to contextual influence than the temporal aspect only. Memories vary in the amount of perceptual, spatial, affective, temporal, as well as semantic information. In accordance with the source-monitoring framework, participants in free recall tasks can use all of these aspects of context information to increase memory performance. In the present study, however, only the temporal aspect of context information was tested. Additional aspects of the study event were thus of no use in determining the correct source. These aspects may explain why improvements in source memory only emerged after WD. An important issue for further research is therefore to examine d-amphetamine facilitation effect on other aspects of context information.

To the best of our knowledge, this was the first study examining the effect of d-amphetamine on temporal aspects of context information in healthy volunteers. Additional research is necessary to further unravel the precise nature of the d-amphetamine facilitation effect on verbal episodic memory. Nevertheless, the present findings are in line with previous results and seem to be in favour of a modulation of the consolidation process of verbal episodic memory by d-amphetamine. An acute administration of d-amphetamine may help feature binding in memory, which in turn may lead to an increased ability to recollect not only the item, but also the source of that item.

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