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ORIGINAL INVESTIGATION

Acute effects of lisdexamfetamine and D-amphetamine on social cognition and cognitive performance in a placebo-controlled study in healthy subjects

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Abstract

Rationale Amphetamines are used as medications but are also misused as cognitive enhancers by healthy subjects and may have additional effects on social cognition.

Methods We investigated the acute effects of single, high, equimolar doses of D-amphetamine (40 mg) and lisdexamfetamine (100 mg) on social cognition and cognitive performance using a randomized, placebo-controlled, double-blind, cross-over design in 24 healthy volunteers. Effects on social cognition were assessed using the Facial Emotion Recognition Task (FERT), Multifaceted Empathy Test (MET), and Sexual Arousal Task (SAT). Cognitive performance was measured using the Digit Symbol Substitution Test (DSST), Digit Span (DS), Stop-Signal Task (SST), and Mackworth Clock Test (MCT).

Results D-Amphetamine and lisdexamfetamine had small effects on measures of social cognition. There were no effects on emotion recognition on the FERT. D-Amphetamine increased direct empathy on the MET, but only for positive stimuli. Both amphetamines increased ratings of pleasantness and attractiveness on the SAT in response to sexual but also to neutral stimuli. D-Amphetamine and lisdexamfetamine increased cognitive performance (go-accuracy and vigilance on the SST and MCT, respectively). Lisdexamfetamine increased processing speed on the DSST. Neither drug had an effect on the DS.

Conclusion Single, high, equimolar doses of D-amphetamine and lisdexamfetamine enhanced certain aspects of cognitive performance in healthy non-sleep-deprived subjects. Both amphetamines also slightly altered aspects of social cognition. Whether these small effects also influence social interaction behavior in amphetamine users remains to be investigated.

Trial registration The study was registered at ClinicalTrials.gov (NCT02668926).

Keywords D-Amphetamine · Lisdexamfetamine · Social cognition · Sexual arousal · Cognitive performance

Introduction

Amphetamines are used as treatments for attention-deficit/hyperactivity disorder (ADHD) but are also misused by healthy subjects for their euphoric effects or to stay awake and enhance cognitive function (Koelega 1993; Liakoni et al. 2015; Maier et al. 2013, 2015; McCabe et al. 2005; Wood et al. 2014). An estimated 1.3 million (1.1%) European adolescents and young adults (15–34 years old) used amphetamines in 2016 (EMCDDA 2017). The lifetime prevalence of amphetamine use in this group ranges from 5.5 to 15% (Johnston et al. 2016). Lisdexamfetamine is a newer inactive prodrug formulation of D-amphetamine (Hutson et al. 2014). Inactive lisdexamfetamine is relatively slowly converted to its active metabolite D-amphetamine in the circulation by enzymatic hydrolysis within red blood cells (Pennick 2010; Sharman and Pennick 2014), thus reducing the subjective effects and risk of parenteral misuse of lisdexamfetamine compared with D-amphetamine. However, when used orally at a high dose, the pharmacokinetics and subjective effects of lisdexamfetamine are

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similar to D-amphetamine, with the exception of a later onset (Dolder et al. 2017c). An increase in reported lisdexamfetamine misuse cases was reported to poison control centers in the United States from 2007 to 2012 (Kaland and Klein-Schwartz 2015).

Amphetamines are thought to increase cognitive and physical performance, attention, and arousal at low to moderate doses, whereas moderate to high doses may produce euphoria and impair cognitive function (Weiss and Laties 1962; Wood et al. 2014). In non-sleep-deprived healthy human subjects, D-amphetamine and methamphetamine can reduce reaction time, sustain a high level of proficiency, and restore deteriorated performance (Weiss and Laties 1962). Studies that assessed the effects of D-amphetamine on different facets of cognitive performance in healthy subjects used low doses (5–20 mg; de Wit et al. 2002; Mackworth 1965; Makris et al. 2007; Wachtel and de Wit 1999; Ward et al. 1997; Weafer and de Wit 2013) or moderate doses (0.42 mg/kg or 25–35 mg; Silber et al. 2006), but the effects of higher doses (> 30 mg) are not well documented. Additionally, lisdexamfetamine increased cognitive performance in multiple sclerosis patients (Morrow et al. 2013), but there are no data on the effects of lisdexamfetamine on cognitive performance in healthy subjects. Therefore, one goal of the present study was to test the performance-enhancing effects of a higher dose of D-amphetamine (40 mg) and an equimolar dose of lisdexamfetamine (100 mg) in healthy subjects. Furthermore, both amphetamines can alter cognitive performance and facets of social cognition, including emotion recognition, empathy, and the perception of sexual stimuli, which has been demonstrated for low-dose D-amphetamine (Wardle et al. 2012) and other psychoactive substances (Dolder et al. 2017b; Hysek et al. 2014a, 2014b; Schmid et al. 2014, 2015b). Specifically, D-amphetamine (Wardle et al. 2012) and methylphenidate (Hysek et al. 2014b; Schmid et al. 2014) both enhance dopamine and norepinephrine neurotransmission (Luethi et al. 2017; Simmler et al. 2013) and were shown to enhance the perception of negative facial expressions. In contrast, serotonergic substances, such as methylenedioxymethamphetamine (MDMA), psilocybin, and lysergic acid diethylamide (LSD), impaired the recognition of negative emotions (Dolder et al. 2017b; Hysek et al. 2014a, 2014b; Kometer et al. 2012; Schmid et al. 2014). Serotonergic substances, such as MDMA, psilocybin, and LSD, were also shown to enhance emotional empathy (Dolder et al. 2016; Hysek et al. 2014a; Kuypers et al. 2017; Pokorny et al. 2017). In contrast, methylphenidate had no effect on empathy (Schmid et al. 2014), and no data are available on D-amphetamine or lisdexamfetamine. Furthermore, the dopaminergic action of stimulants is proposed to increase sexual arousal, which has been reported for methylphenidate, methamphetamine, and cocaine (Frohmader et al. 2010; Rawson et al. 2002; Schmid et al. 2015b; Volkow et al. 2007). Therefore, D-amphetamine and lisdexamfetamine can be expected to also enhance sexual arousal. However, to our knowledge, no data are available on sexual arousal following lisdexamfetamine or D-amphetamine administration in healthy subjects. With the exception of the effects of low-dose D-amphetamine on emotion recognition, little is known about the acute effects of D-amphetamine on other aspects of social cognition, with no data on lisdexamfetamine.

The present clinical trial was mainly designed to compare the single-dose pharmacokinetics and pharmacodynamics (subjective, cardiovascular, and endocrine effects over time) of lisdexamfetamine and D-amphetamine. These results are reported in detail elsewhere (Dolder et al. 2017c) and selected subjective effects also shown here. An additional goal of the present study was to investigate the effects of both amphetamines on facets of social cognition (emotion recognition, empathy, and sexual arousal) and cognitive performance (processing speed, memory, response inhibition, and vigilance) compared with placebo. The study was not designed to assess differences between the two amphetamines. The predefined study hypotheses in the clinical study protocol were that both lisdexamfetamine and D-amphetamine compared with placebo would (1) not impair the recognition of negative emotions (fear, sadness) on the Facial Emotion Recognition Task (FERT), (2) not enhance emotional empathy on the Multifaceted Empathy Test (MET), and (3) enhance sexual arousal on the Sexual Arousal Task (SAT), which has been shown for methylphenidate but not MDMA (Dolder et al. 2017b; Hysek et al. 2014a, 2014b; Schmid et al. 2014, 2015b). Additionally, we expected that both lisdexamfetamine and D-amphetamine would enhance cognitive performance on the Digit Symbol Substitution Test (DSST), Digit Span (DS), Stop-Signal Task (SST), and Mackworth Clock Test (MCT) compared with placebo and consistent with the use of amphetamine-type stimulants by healthy subjects as cognitive enhancers (Kaland and Klein-Schwartz 2015; Liakoni et al. 2015; Maier et al. 2013, 2015; McCabe et al. 2005).

Methods

Study design

The present study used a randomized, placebo-controlled, double-blind, cross-over design with three experimental test days (40 mg D-amphetamine, 100 mg lisdexamfetamine, and placebo) in balanced order. The washout periods between sessions were at least 7 days. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines in Good Clinical Practice and approved by the Ethics Committee northwest/central Switzerland (EKNZ) and Swiss Agency for Therapeutic Products (Swissmedic). All of the subjects

provided written consent before participating in the study, and they were paid for their participation. The study was registered at ClinicalTrials.gov (NCT02668926).

Participants

Twenty-four healthy subjects (12 men, 12 women), mean ± SD age of 25.3 ± 3.0 years (range, 21–34 years), were recruited from the University of Basel. All of the participants were university students with at least a bachelor's degree (13 subjects), master's degree (10 subjects), or PhD equivalent (1 subject). All participants were heterosexual. The inclusion criteria were age 18–45 years, body mass index 18–27 kg/m^2, and birth control for women. Subjects with a personal or first-degree-relative history of psychiatric disorders (determined by the structured clinical interview for Axis I and Axis II disorders according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; Wittchen et al. 1997) were excluded. Physical health was assessed by medical history, physical examination, electrocardiogram, standard hematology, and chemical blood analyses and subjects with chronic or acute physical illness were excluded. Additional exclusion criteria were pregnancy determined by a urine test at screening and before each test session, tobacco smoking (> 10 cigarettes/day), the consumption of alcoholic drinks (> 10/week), and a lifetime history of using illicit drugs more than five times, with the exception of occasional cannabis use in the past. Subjects who used any illicit drugs, including cannabis, within the past 2 months or during the study period were excluded. The subjects were asked to abstain from excessive alcohol consumption between test sessions (no more than 10 drinks/week and only one drink on the day before the session) and not to drink caffeine-containing liquids after midnight before the study day. We performed drug tests at the screening visit and before each test session using TRIAGE 8 (Biosite, San Diego, CA, USA). Female subjects were investigated during the follicular phase of their menstrual cycle (day 2–14 according to the women with day 1 being the first day of menstrual bleeding) to account for cyclic changes in the reactivity to D-amphetamine (White et al. 2002).

Study procedures

The study included a screening visit, three experimental sessions (test days), and an end-of-study visit. Experimental sessions began at 8:00 AM. An indwelling intravenous catheter was placed in an antecubital vein for blood sampling. A single dose of D-amphetamine, lisdexamfetamine, or placebo was administered at 9:00 AM. For the analysis of amphetamine concentrations in plasma, blood samples were collected in lithium heparin tubes 1 h before and 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, and 24 h after drug administration. The blood samples were immediately centrifuged, and the plasma was rapidly stored at − 20 °C and later at − 80 °C until analysis. The test session ended at 9:00 PM. The subjects returned home and returned the following day at 9:00 AM for the final 24-h measurements and drawing of blood samples.

Study drugs

Identical gelatin capsules that contained either lisdexamfetamine dimesylate (100 mg salt; Opopharma, Rümlang, Switzerland) or D-amphetamine sulfate (40.3 mg salt; Hänseler, Herisau, Switzerland), both corresponding to an equivalent dose of 29.6 mg D-amphetamine, and placebo capsules (mannitol) were prepared by the pharmacy of the University Hospital Basel according to Good Manufacturing Practice. To mimic misuse of the substances as cognitive enhancers, the doses were relatively high and above the upper recommended daily dose of 70 mg lisdexamfetamine.

Plasma concentrations of amphetamine

Plasma concentrations of amphetamine were measured by ultra-high-pressure liquid chromatography–mass spectrometry/mass spectrometry as reported elsewhere (Dolder et al. 2017c). Plasma concentrations of amphetamine after the administration of lisdexamfetamine and D-amphetamine during the different times of testing were estimated for each participant using compartmental modeling and Phoenix WinNonlin 6.4 (Certara, Princeton, NJ, USA) as shown in detail elsewhere (Dolder et al. 2017c).

Subjective effects

Visual Analog Scales (VASs) were repeatedly used to assess subjective effects over time. The VASs included "good drug effect," "stimulated," and "alertness". The VASs were presented as 100-mm horizontal lines (0 to + 100), marked from "not at all" on the left to "extremely" on the right. The VASs were administered 1 h before and 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 h after drug administration.

Tests of social cognition

Facial Emotion Recognition Task We used the FERT, which has been used with related psychostimulants, including MDMA (Bedi et al. 2010; Dolder et al. 2017b; Hysek et al. 2014a; Schmid et al. 2014) and methylphenidate (Dolder et al. 2017b; Hysek et al. 2014b; Schmid et al. 2014). The task included 10 neutral faces and 160 faces that expressed one of four basic emotions (i.e., happiness, sadness, anger, and fear), with pictures morphed between 0% (neutral) and 100% in 10% steps. Two female and two male pictures were used for each of the four emotions. The stimuli were presented

in random order for 500 ms and then were replaced by the rating screen where participants had to indicate the correct emotion. The main outcome measure was accuracy (proportion correct). Additionally, we analyzed whether incorrectly identified emotional expressions were misclassified as neutral or other emotions (Bedi et al. 2010; Schmid et al. 2014). The FERT was performed 3 h after drug administration.

Multifaceted Empathy Test The MET is a reliable and valid task that assesses the cognitive and emotional aspects of empathy (Dziobek et al. 2008). The MET was sensitive to oxytocin (Hurlemann et al. 2010) and MDMA (Hysek et al. 2014a; Kuypers et al. 2017; Schmid et al. 2014), whereas methylphenidate had no effects (Schmid et al. 2014). The computer-assisted test consisted of 40 photographs that showed people in emotionally charged situations. To assess cognitive empathy, the participants were required to infer the mental state of the subject in each scene and indicate the correct mental state from a list of four responses. Cognitive empathy was defined as the percentage of correct responses relative to total responses. To measure emotional empathy, the subjects were asked to rate how much they were feeling for an individual in each scene (i.e., explicit emotional empathy) and how much they were aroused by each scene (i.e., implicit emotional empathy) on a 1–9 point scale. The latter rating provides an inherent additional assessment of emotional empathy, which is considered to reduce the likelihood of socially desirable answers. The three aspects of empathy were each tested with 20 stimuli with positive valence and 20 stimuli with negative valence, resulting in a total of 120 trials. The MET was performed 3.25 h after drug administration.

Sexual Arousal Task The SAT assesses sexual arousal following implicit and explicit sexual stimuli and has recently been shown to be sensitive to methylphenidate (Schmid et al. 2015b) and alcohol (Dolder et al. 2017a). The SAT included 16 color photographs from the International Affective Picture System (IAPS; Lang et al. 2008), as similarly used by others (Aguilar de Arcos et al. 2008). There were eight neutral and eight erotic or sexual pictures. Neutral pictures showed landscapes, objects, or people without sexual signals. Erotic pictures included four implicit sexual scenes (i.e., no primary or secondary sexual organs are shown explicitly, but the people in the pictures were shown in stimulating poses that revealed some skin) and four explicit sexual scenes (i.e., clearly pornographic poses or scenes). In the neutral, implicit, and explicit conditions (valence), two pictures with an individual person and two pictures with couples were shown, respectively. Thus, we had four pictures of neutral objects (two pictures) and landscapes (two pictures), four pictures of neutral people (two pictures of individual people and two pictures of couples), four pictures of implicit sexual scenes (two pictures of individual people and two pictures of couples), and four pictures of explicit erotic scenes (two pictures of individual people and two pictures of couples). Additionally, there were male and female versions of the test. Female subjects were only shown pictures of males in the single-person condition, and male subjects were only shown pictures of females in the single-person condition. Because men and women were tested on different tasks, the scores could not be compared directly. The participants were asked to rate each picture on five dimensions (adjectives). The dimensions included "pleasant," "arousing/exciting," "attractive," "likeable," and "erotic." The original Self-Assessment Manikin was used for the affective dimensions valence ("pleasant") and arousal ("arousing/exciting"; Bradley and Lang 1994), resulting in a 9-point rating scale. Ratings for "attractive," "likeable," and "erotic" were made on a 9-point rating scale, marked "not at all" on the left to "very" on the right. Ratings of all neutral, implicit sexual, and explicit sexual pictures were averaged for each dimension. The SAT was administered using Presentation 14.8 software (Neurobehavioral Systems, Albany, CA, USA) and presented on a computer screen. The SAT was administered 3.5 h after drug administration.

Cognitive performance tests

Digit Symbol Substitution Test The DSST is a processing speed test and part of the Wechsler Adult Intelligence Scale (WAIS; Wechsler 1939). The DSST was sensitive to methamphetamine (Silber et al. 2006), D-amphetamine (de Wit et al. 2002; Makris et al. 2007; Wachtel and de Wit 1999; Ward et al. 1997), and modafinil (Makris et al. 2007) in healthy subjects and sensitive to lisdexamfetamine and mixed amphetamine salts in patients with multiple sclerosis (Morrow and Rosehart 2015; Morrow et al. 2013). The test consisted of nine fixed symbols that were matched to the numerals/digits 1–9. The subjects were instructed to match the symbol that was shown with the appropriate number as fast as possible. They were given 120 s to complete as many trials as possible. Prior to the test, every subject was given 20 s to practice the task and complete some test trials. The main outcome was the number of correct responses. The DSST was administered 3.75 h after drug administration.

Digit Span The DS is part of the WAIS (Wechsler 1939) and typically used to assess working memory and concentration. It has been shown to be sensitive to lower (10 and 20 mg) but not higher (0.42 mg/kg) doses of D-amphetamine (de Wit et al. 2002; Silber et al. 2006). It was also sensitive to the effects of methylphenidate in healthy subjects and ADHD patients (Agay et al. 2010; van der Schaaf et al. 2013). We used a computer-based version of the DS. Numbers were read aloud, and the participants had to recall them correctly. There were two different subtasks: forward task and backward task. In the forward task (starting with three digits), the subjects had

to recall numbers in the original order. In the backward task (starting with two digits), they had to recall the numbers in reverse order. In contrast to the WAIS method, in which the task ends after two incorrect responses, the participants in the present study completed 14 trials in the forward task and 14 trials in the backward task using the staircase method. If a row was recalled correctly, then the span was increased by one digit. After two incorrect responses, the span was decreased by one digit. This staircase method has several advantages (Woods et al. 2011). It allows the determination of individual participants' true maximum length and accounts for distractions or idiosyncratically difficult digit strings (Woods et al. 2011). The main task outcome was the combined total span of both subtasks. The DS was administered 4 h after drug administration.

Stop-Signal Task The SST is used to assess executive control and study response inhibition in a laboratory setting (Lappin and Eriksen 1966; Logan et al. 1984). Alterations in executive control have been described in various clinical conditions, such as substance use disorder (de Wit 2009), pathological gambling (Zack et al. 2017), and ADHD (Rapport et al. 1985; Tannock et al. 1989). These patients presented impairments on the SST (Tannock et al. 1989; Zack et al. 2017) but exhibited improvements following the administration of methylphenidate (Aron et al. 2003; Boonstra et al. 2005), modafinil (Turner et al. 2004), or D-amphetamine (Zack et al. 2017). In contrast, no effects were reported in smaller studies of D-amphetamine in healthy volunteers (de Wit et al. 2000; de Wit et al. 2002; Fillmore et al. 2005). A larger pooled study in 165 subjects reported enhanced response inhibition (Weafer and de Wit 2013). The SST's core feature has been described as a race between a "go" and a "stop" process (Logan et al. 1984; Verbruggen and Logan 2008). The "go" process results in pressing a button, whereas the "stop" process results in inhibition of the response. If the "go" process finishes first, then the result will be a continuation. If the "stop" process finishes first, then an inhibition of action will result. The estimated time between presentation of the stop signal and successful inhibition is the "Stop-Signal Reaction Time," which can be assessed by looking at the range of times that each individual needs for successful and unsuccessful inhibition (Verbruggen and Logan 2008). The time between presentation of the "go" and "stop" signals is the "Stop-Signal Delay" (SSD). The SSD increases following correct trials and decreases following incorrect trials. Principally, a stop signal that appears more rapidly after presentation of the "go" signal is easier to inhibit. We used a computer-based test, with the presentation of two stimuli ("A" and "Z") and a stop signal ("X"). A total of 200 trials were presented, with 40 total stop trials that were evenly split between both stimuli. The subjects were instructed to press the left computer mouse button when "A" was presented, press the right mouse button when "Z" was presented, and inhibit the response when "X" (the stop signal) was presented. Before each session, the subjects completed a set of practice trials. If they did not achieve 50% correct responses, then practice trials were run again until this criterion was met. The starting SSD was 400 ms, which was then adjusted based on the subject's performance in the practice trials. If the subject successfully inhibited their response after a stop trial, then the SSD was increased by 17 ms. After unsuccessful inhibition, the SSD was decreased by 17 ms. The Stop-Signal Reaction Time was then calculated for each subject by subtracting the final SSD from the median response time. The main outcomes of the test were the accuracies of the stop and go signals and the Stop-Signal Reaction Time. The SST was administered 4.25 h after drug administration.

Mackworth Clock Test The MCT was used to measure vigilance performance, an ability to focus on critical signals over time (Mackworth 1948). The MCT was sensitive to the effects of caffeine (Wilhelmus et al. 2017), methylphenidate (Theunissen et al. 2009), modafinil (Theunissen et al. 2009), and D-amphetamine (Mackworth 1965) in healthy subjects. The total duration of the task was shortened to 10 min as it was administered as the last of all social-cognitive and performance tests after a total testing duration of 2 h. The clock was represented by 50 gray dots in a circle. One of the dots was highlighted for 400 ms in color (stimulus) in clockwise order with an inter-stimulus interval of 400 ms. The proportion of trials in which a dot was skipped was set to 0.075. Each skip was followed by at least five consecutive non-skip trials. The subjects were told that each dot will be highlighted in continuous (clockwise) order and that they should press the mouse button if one dot was skipped. The outcome measures were the accuracy of correct responses, misses, and the number of false alarms. The MCT was administered 4.5 h after drug administration.

Statistical analyses

The data were analyzed using repeated-measures analysis of variance (ANOVA), with drug as the within-subjects factor for each scale. The subjective effect measures that were repetitively assessed over time were expressed as E_{max} values prior to the ANOVA. The SAT ratings were also analyzed using ANOVA with sexual content (neutral, implicit, explicit) as additional within-subjects factor to assess whether the drug effects depend on the content of the stimulus. Tukey post hoc comparisons were performed based on significant main effects of drug. Pearson correlations were used to assess relationships between plasma amphetamine concentrations at the time of testing and changes in cognitive performance after lisdexamfetamine and D-amphetamine administration compared with placebo (placebo-adjusted values). The criterion for significance was $p < 0.05$.

Results

All statistics are shown in Tables 1 and 2.

Subjective effects

Subjective drug effects over time are shown in Fig. 1. Lisdexamfetamine and D-amphetamine produced similar increases in VAS scores for "good drug effects," "stimulated," and "alertness" compared with placebo (Table 1, Fig. 1). The subjective drug effect–time curves were shifted to the right (Fig. 1) consistent with significantly longer time to onset and time to maximal effect values after lisdexamfetamine administration compared with D-amphetamine administration, consistent with the pharmacokinetics of the two drugs (Dolder et al. 2017c). However, no differences in E_{max} values were found between lisdexamfetamine and D-amphetamine (Table 1). The pharmacokinetics and additional pharmacodynamic effects are reported in detail elsewhere (Dolder et al. 2017c).

Tests of social cognition

Facial Emotion Recognition Task D-Amphetamine and lisdexamfetamine had no significant effects on the FERT. The correct recognition of neutral, happy, sad, angry, and fearful faces was not significantly altered compared with placebo (Table 1). Similarly, neither drug affected the misclassification of emotions.

Multifaceted Empathy Task D-Amphetamine significantly increased direct emotional empathy only for the subset of positive stimuli but not for negative stimuli or for all stimuli together compared with placebo (Table 1). Consistently, ANOVA with drug and valence (positive vs. negative) as factors showed a trend interaction of drug and valence ($F_{2,46}$ = 2.92, p = 0.06). Lisdexamfetamine did not alter emotional empathy. Neither D-amphetamine nor lisdexamfetamine increased the correct identification of complex emotions (cognitive empathy).

Sexual Arousal Task The ANOVA revealed significant main effects of sexual content (neutral, implicit, explicit) on all ratings (all $F_{2,46} > 10$, $p < 0.001$), with higher ratings for sexual content compared with neutral content. The ANOVAs that were conducted for each rating separately, with drug as the factor, indicated that after lisdexamfetamine administration, the subjects rated pictures with explicit sexual content as "more pleasant" compared with placebo (Table 1). There was also a trend toward the subjects' rating the pictures with implicit sexual content as more pleasant following lisdexamfetamine ($p = 0.09$) or D-amphetamine ($p = 0.08$) administration compared with placebo. Implicit sexual pictures were rated as significantly "more attractive" following D-amphetamine administration compared with placebo (Table 1), with a similar trend toward an effect following lisdexamfetamine administration ($p = 0.08$). There was a trend toward the subjects' rating implicit sexual stimuli as more erotic after D-amphetamine administration ($p = 0.06$) compared with placebo. However, neutral images were also rated as more attractive after D-amphetamine ($p < 0.05$) and lisdexamfetamine ($p < 0.01$) administration compared with placebo. Consistently, ANOVAs including drug and sexual content (neutral, implicit, explicit) revealed significant main effects of drug on ratings of pleasant and attractive ($F_{2,46}$ = 5.04, $p < 0.05$, and $F_{2,46} = 6.96$, $p < 0.01$, respectively), with no drug × sexual content interactions. Thus, lisdexamfetamine and D-amphetamine increased pleasant and attractive ratings of the pictures, regardless of content.

Cognitive performance tests

Digit Symbol Substitution Test Lisdexamfetamine significantly increased the number of completed trials and number of correct responses compared with placebo (Table 2, Fig. 2). Response accuracy was similar for all drug conditions. D-Amphetamine had no effects on any of the DSST test measures compared with placebo.

Digit Span Data were missing from one subject in one session because of technical problems. No effects of either drug on the total span were found (Table 2, Fig. 2).

Stop-Signal Task Data were missing from one subject in one session because of technical problems. No effects of either drug on the Stop-Signal Reaction Time were found. The accuracy in go-trials significantly increased after lisdexamfetamine and D-amphetamine administration compared with placebo (Table 2, Fig. 2).

Mackworth Clock Test Data from three participants could not be used because the test was not used in one participant and the instructions were misunderstood by two participants. Both lisdexamfetamine and D-amphetamine significantly increased response accuracy and decreased the number of misses and false alarms (Table 2, Fig. 2).

Plasma amphetamine concentrations during testing

Maximal plasma amphetamine concentrations were reached 3.3 and 4.6 h after D-amphetamine and lisdexamfetamine administration, respectively, during the time of testing (Fig. 3) and as reported elsewhere in detail (Dolder et al. 2017c). Plasma amphetamine concentrations after D-amphetamine administration increased earlier compared with lisdexamfetamine (Dolder et al. 2017c). Specifically, the

Table 1 Effects on social cognitive tests (mean ± SEM values and statistics)

		Placebo	Lisdexamfetamine	D-Amphetamine	Main effect of drug		Partial eta-squared
		(mean ± SEM)	(mean ± SEM)	(mean ± SEM)	$F_{2,46}$	p	η^2
Visual Analog Scale (VAS, %max)							
Good drug effect	E_{max}	4.0 ± 2.5	42 ± 6.5***	49 ± 5.6***	36.65	< 0.001	0.62
Stimulated	E_{max}	2.4 ± 1.7	38 ± 6.9***	44 ± 5.7***	24.97	< 0.001	0.53
Alertness	E_{max}	2.4 ± 1.1	50 ± 7.2***	56 ± 6.4***	41.31	< 0.001	0.65
Facial Emotion Recognition Task							
Neutral	% correct	67.9 ± 3.2	68.3 ± 3.3	69.2 ± 3.1	0.05	NS	0.00
Happy	% correct	55.3 ± 2.3	57.9 ± 1.9	57.7 ± 2.2	1.01	NS	0.04
Sad	% correct	41.8 ± 2.3	41.7 ± 2.0	40.6 ± 2.3	0.15	NS	0.01
Anger	% correct	57.5 ± 1.5	56.8 ± 1.5	56.2 ± 1.2	0.27	NS	0.01
Fear	% correct	52.4 ± 1.6	50.8 ± 1.8	54.9 ± 1.5	2.08	NS	0.08
Multifaceted Empathy Test							
Direct emotional empathy							
All stimuli	Rating	4.93 ± 0.20	5.07 ± 0.26	5.24 ± 0.22	1.68	NS	0.06
Positive stimuli	Rating	4.63 ± 0.20	4.88 ± 0.33	5.20 ± 0.27*	3.29	< 0.05	0.13
Negative stimuli	Rating	5.24 ± 0.25	5.27 ± 0.28	5.28 ± 0.26	0.02	NS	0.00
Indirect emotional empathy							
All stimuli	Rating	4.62 ± 0.20	4.72 ± 0.25	4.83 ± 0.21	0.76	NS	0.03
Positive stimuli	Rating	4.29 ± 0.21	4.53 ± 0.28	4.58 ± 0.24	1.30	NS	0.05
Negative stimuli	Rating	4.94 ± 0.24	4.91 ± 0.27	5.08 ± 0.24	0.40	NS	0.02
Cognitive empathy							
All stimuli	Number correct	26.1 ± 0.6	26.6 ± 0.6	27.1 ± 0.6	1.47	NS	0.06
Positive stimuli	Number correct	13.8 ± 0.3	14.3 ± 0.3	14.2 ± 0.3	1.32	NS	0.05
Negative stimuli	Number correct	12.3 ± 0.5	12.3 ± 0.5	12.9 ± 0.4	1.34	NS	0.06
Sexual Arousal Task							
Neutral pleasant	Rating	5.73 ± 0.12	5.89 ± 0.17	5.73 ± 0.18	0.86	NS	0.04
Sexual explicit pleasant	Rating	5.45 ± 0.21	5.89 ± 0.22**	5.59 ± 0.23	5.46	< 0.01	0.19
Sexual implicit pleasant	Rating	6.52 ± 0.18	6.76 ± 0.17	6.77 ± 0.17	3.16	NS	0.12
Neutral exciting	Rating	3.52 ± 0.16	3.61 ± 0.18	3.36 ± 0.19	1.15	NS	0.05
Sexual explicit exciting	Rating	6.15 ± 0.23	6.41 ± 0.24	6.19 ± 0.29	1.17	NS	0.05
Sexual implicit exciting	Rating	5.78 ± 0.19	5.9 ± 0.26	5.57 ± 0.25	1.13	NS	0.05
Neutral attractive	Rating	3.98 ± 0.18	4.38 ± 0.21**	4.43 ± 0.20*	6.34	< 0.01	0.22
Sexual explicit attractive	Rating	5.38 ± 0.28	5.56 ± 0.31	5.54 ± 0.33	0.74	NS	0.03
Sexual implicit attractive	Rating	6.50 ± 0.20	6.77 ± 0.17	6.90 ± 0.19**	5.37	< 0.01	0.19
Neutral likeable	Rating	4.16 ± 0.22	4.30 ± 0.23	4.43 ± 0.24	1.99	NS	0.08
Sexual explicit likeable	Rating	4.67 ± 0.23	4.76 ± 0.25	4.82 ± 0.28	0.43	NS	0.02
Sexual implicit likeable	Rating	6.11 ± 0.2	6.2 ± 0.26	6.38 ± 0.25	2.14	NS	0.09
Neutral erotic	Rating	3.04 ± 0.17	3.06 ± 0.22	3.17 ± 0.25	0.41	NS	0.02
Sexual explicit erotic	Rating	5.94 ± 0.32	5.98 ± 0.34	6.02 ± 0.35	0.12	NS	0.01
Sexual implicit erotic	Rating	5.73 ± 0.28	6.06 ± 0.23	6.14 ± 0.22	3.05	NS	0.12

Values are mean ± SEM in 24 subjects

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, *NS* not significant compared to placebo

increase in plasma amphetamine concentrations had a 0.6 ± 0.6 h (mean ± SD) longer lag time and reached peak levels 1.1 ± 1.5 h later after lisdexamfetamine administration compared with D-amphetamine (Dolder et al. 2017c). This resulted in significantly higher plasma concentrations of amphetamine after D-amphetamine compared with lisdexamfetamine at 3 and 3.25 h during the FERT and MET tests ($F_{1,21} = 7.97$ and 5.05, respectively, both $p < 0.05$),

Table 2 Effects on cognitive performance tests (mean ± SEM values and statistics)

		Placebo	Lisdexamfetamine	D-Amphetamine	Main effect of drug		Partial eta-squared
		(mean ± SEM)	(mean ± SEM)	(mean ± SEM)	$F_{2,46}$	p	η^2
Digit Symbol Substitution Test (DSST)					$F_{2,46}$		
Number of trials	n	66.96 ± 2.0	72.04 ± 2.3*	67.63 ± 2.0	4.35	< 0.05	0.16
Correct responses	n	64.63 ± 1.9	69.79 ± 2.2*	65.13 ± 1.9	4.61	< 0.05	0.17
Accuracy	(%)	97 ± 1	97 ± 0	96 ± 0	0.31	NS	0.01
Digit Span (DS)					$F_{2,44}$		
Total span	n	15.39 ± 0.56	15.83 ± 0.55	15.26 ± 0.41	0.6	NS	0.03
Stop Signal Task (SST)					$F_{2,44}$		
Stop-Signal Reaction Time	ms	216 ± 16	211 ± 11	205 ± 15	0.72	NS	0.03
Accuracy Go Trials	(%)	96 ± 1	98 ± 1*	98 ± 1*	4.09	< 0.05	0.16
Accuracy Stop Trials	(%)	62 ± 4	71 ± 5	68 ± 4	2.96	NS	0.12
Mackworth Clock Test (MCT)					$F_{2,40}$		
Accuracy	(%)	93 ± 2	99 ± 1**	98 ± 0**	8.87	< 0.001	0.31
Misses	n	3.95 ± 1.10	0.62 ± 0.32**	1.00 ± 0.25**	8.68	< 0.001	0.30
False alarms	n	2.62 ± 0.62	0.71 ± 0.30**	1.24 ± 0.34*	7.05	< 0.01	0.26

Values are mean ± SEM in 24, 23, 23, and 21 subjects for the DSST, DS, SST, and MCT, respectively

*$p < 0.05$, **$p < 0.01$, *NS* not significant compared to placebo

respectively, but no or only minimal differences at 3.5–4.75 h when the other tests were performed (Fig. 3).

Association between plasma amphetamine concentrations and cognitive test performance

Higher plasma amphetamine concentrations during the DSST at 3.75 h were significantly and inversely correlated with the increase in correct responses on the DSST after lisdexamfetamine and D-amphetamine administration compared with placebo ($R_p = -0.47$, $p < 0.05$, $n = 24$ and $R_p = -0.53$, $p < 0.01$, $n = 23$, respectively; Fig. S1). Similarly, higher plasma amphetamine concentrations during the MCT at 4.5 h were inversely correlated with the increase in response accuracy that was induced by lisdexamfetamine and D-amphetamine compared with placebo ($R_p = -0.37$, NS, $n = 21$ and $R_p = -0.45$, $p < 0.05$, $n = 20$, respectively; Fig. S2). During the MCT, amphetamine concentrations after lisdexamfetamine and D-amphetamine were non-significantly correlated with the number of misses ($R_p = 0.38$, NS, $n = 21$ and $R_p = 0.43$, NS, $n = 20$, respectively; Fig. S3) and significantly correlated with the number of false alarms ($R_p = 0.50$, $p < 0.05$, $n = 21$ and $R_p = 0.49$, $p < 0.05$, $n = 20$, respectively; Fig. S4). Thus, within the dose range tested and within the treatment condition, higher exposure to amphetamine impaired performance on these tasks although performance was enhanced when compared to the placebo condition.

Discussion

The administration of relatively high and equimolar doses of D-amphetamine and lisdexamfetamine in healthy subjects had no or only minimal effects on measures of social cognition, including the FERT, MET, and SAT, but enhanced aspects of cognitive performance on the DSST, SST, and MCT. Both amphetamines also enhanced subjective mood and stimulation.

As hypothesized, neither amphetamine altered the identification of basic facial emotional expressions on the FERT or impaired the recognition of negative emotions (fear, sadness), similar to the dopamine uptake inhibitor methylphenidate (Dolder et al. 2017b; Hysek et al. 2014b; Schmid et al. 2014) and in contrast to the more serotonergic amphetamine derivative MDMA (Bedi et al. 2010; Dolder et al. 2017b; Hysek et al. 2014b; Kirkpatrick et al. 2014; Schmid et al. 2014). However, in contrast to our study hypothesis, D-amphetamine increased emotional empathy for positive emotional stimuli, similar to MDMA (Hysek et al. 2014a; Kuypers et al. 2017) but unlike methylphenidate (Schmid et al. 2014). The finding of enhanced empathy indicates that D-amphetamine may share some empathogenic properties that are typically attributed to MDMA (Bershad et al. 2016; Hysek et al. 2014a) and other serotonergic drugs (Dolder et al. 2016; Pokorny et al. 2017; Schmid et al. 2015a) but not to more stimulant-type dopaminergic drugs (Bershad et al. 2016; Dolder et al. 2017b; Hysek et al. 2014b).

Lisdexamfetamine and D-amphetamine also resulted in marked subjective positive mood effects that were comparable

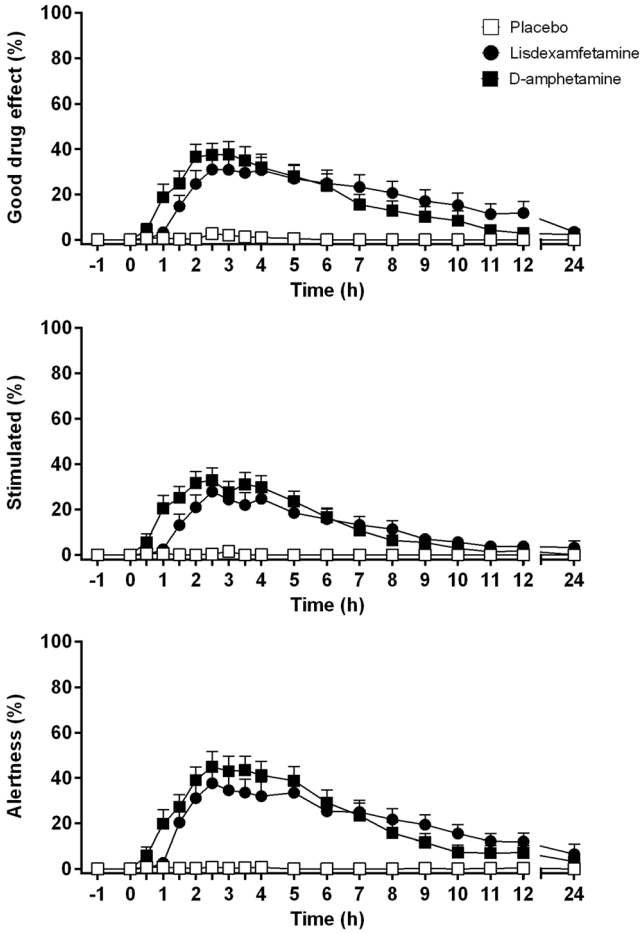

Fig. 1 Subjective effects of lisdexamfetamine and D-amphetamine compared with placebo. The effect onset and maximal response were non-significantly delayed after lisdexamfetamine administration compared with D-amphetamine administration, but the maximal effects and curve shapes were similar. The data are expressed as the mean ± SEM in 24 subjects

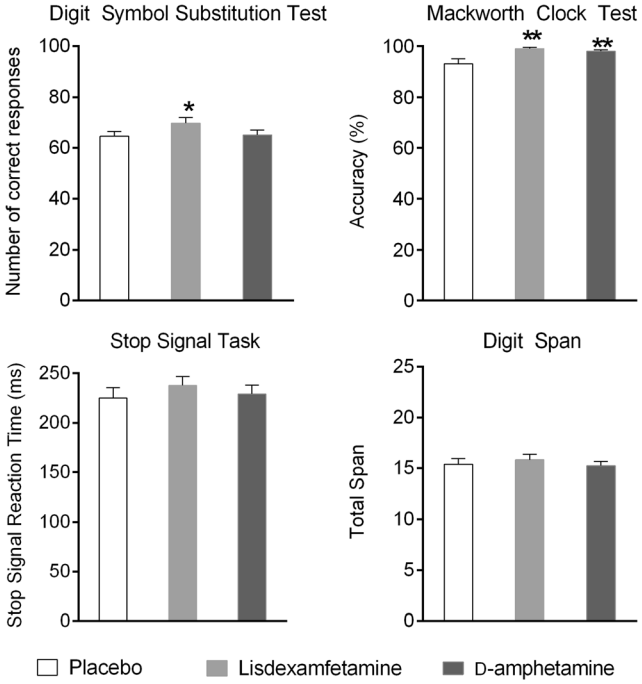

Fig. 2 Effect of lisdexamfetamine, D-amphetamine, and placebo on cognitive performance. In the Digit Symbol Substitution Test (DSST), lisdexamfetamine significantly increased cognitive processing speed (number of correct responses) compared with placebo (*$p < 0.05$). In the Mackworth Clock Test (MCT), both lisdexamfetamine and D-amphetamine significantly increased vigilance (response accuracy) compared with placebo (**$p < 0.01$). No significant differences in drug effects were observed on the Stop-Signal Task (SST), a measure of response inhibition, or on the Digit Span (DS), a measure of memory capacity. The DSST was administered 3.75 h after drug administration, and the data are expressed as the mean and SEM in 24 subjects. The MCT was administered 4.5 h after drug administration, and the data are expressed as the mean and SEM in 21 subjects. The SST and DS were administered 4.25 and 4 h after drug administration, respectively, and the data are expressed as the mean and SEM in 23 subjects

to those of 75 mg of MDMA (Vizeli and Liechti 2017) or 60 mg of methylphenidate (Schmid et al. 2014) but lower than those of 125 mg of MDMA (Vizeli and Liechti 2017). It is possible that the increase in empathy for positive stimuli after administration of D-amphetamine or MDMA partly reflects an enhanced responsivity to rewarding stimuli as a function of enhanced mood. However, oxytocin has been shown to induce empathy in the MET in the absence of subjective effects (Hurlemann et al. 2010) and methylphenidate had no effects on empathy in the MET in the presence of significant positive mood effects (Schmid et al. 2014).

In contrast to the study hypothesis and the effects of methylphenidate, which has been shown to enhance sexual arousal ratings for sexually explicit stimuli (Schmid et al. 2015b), lisdexamfetamine and D-amphetamine did not robustly enhance sexual arousal on the SAT. Lisdexamfetamine increased pleasant ratings for sexual explicit stimuli, and D-amphetamine increased attractive ratings for sexual implicit stimuli. However, both drugs also increased attractive ratings for neutral stimuli. Overall, both amphetamines tended to increase arousal ratings for all pictures on the SAT, regardless of sexual content. Overall, these effects of the two amphetamines on measures of social cognition were moderate, with effects on the FERT and SAT that were more similar to methylphenidate than to MDMA and effects on the MET that were more similar to MDMA than to methylphenidate.

Using the FERT, we previously showed that methylphenidate dose-dependently increased the recognition of happy, sad, and fearful facial expressions, with no significant effects at 40 mg and significant effects at 60 mg (Hysek et al. 2014b; Schmid et al. 2014). A similar decrease in the threshold for identifying positive and negative emotions was reported after the administration of 20 mg D-amphetamine on another FERT (Wardle et al. 2012). However, no such effects were found in the present study that assessed the effects of comparably high single doses of 40 mg D-amphetamine. MDMA selectively impaired the recognition of negative emotions, including sadness, anger, and fear, on the FERT (Schmid et al. 2014), an

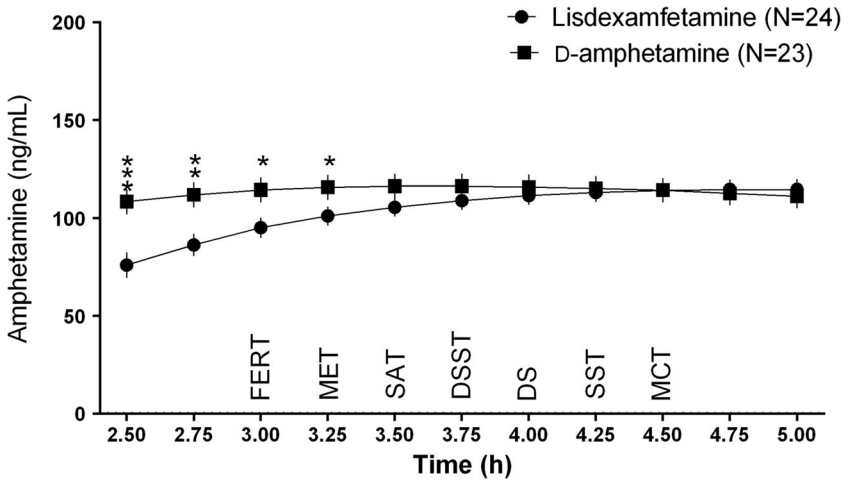

Fig. 3 Plasma amphetamine concentration–time profile following administration of lisdexamfetamine and D-amphetamine during social cognition and cognitive test performance. Amphetamine concentrations were significantly lower after the administration of lisdexamfetamine compared with D-amphetamine at 2.50 h (***$p < 0.001$), 2.75 h (**$p < 0.01$), 3.0 h (*$p < 0.05$), and 3.25 h (*$p < 0.05$) during the FERT and MET but not thereafter during the SAT or cognitive performance testing (3.5–4.75 h). FERT, Facial Emotion Recognition Task; MET, Multifaceted Empathy Test; SAT, Sexual Arousal Task; DSST, Digit Symbol Substitution Test; DS, Digit Span; SST, Stop-Signal Task; MCT, Mackworth Clock Test. The amphetamine concentrations represent the mean and SEM of individual curves fitted to the observed data using a one-compartment model as reported in detail elsewhere (Dolder et al. 2017c)

effect that was clearly distinct from the dopaminergic amphetamines in the present study. Thus, the results are consistent with the notion of distinct effects of D-amphetamine and MDMA on emotion recognition (Bershad et al. 2016; Dolder et al. 2017b). Lower activation of the amygdala by negative emotional stimuli has been described after the acute administration of MDMA (Bedi et al. 2009) and other serotonergic substances (Kraehenmann et al. 2015; Mueller et al. 2017). The acute administration of D-amphetamine increased negative facial responses to sad expressions in healthy subjects (Wardle et al. 2012), and amygdala hyperreactivity to fearful facial expressions was observed in D-amphetamine users (Bottelier et al. 2015).

MDMA is a releaser of serotonin and oxytocin and has been repeatedly shown to enhance empathy, particularly for positive stimuli on the MET (Hysek et al. 2014a; Kuypers et al. 2014, 2017; Schmid et al. 2014), an empathogenic effect that has also been reported for oxytocin (Hurlemann et al. 2010) and other serotonergic substances (Dolder et al. 2016; Pokorny et al. 2017) but not for substances that enhance dopaminergic neurotransmission, such as methylphenidate (Schmid et al. 2014). D-Amphetamine mainly releases dopamine and norepinephrine and not serotonin (Simmler et al. 2013). An unexpected finding in the present study was that D-amphetamine also enhanced emotional empathy for positive stimuli on the MET. However, lisdexamfetamine and D-amphetamine produced acute drug effects in the present study, including mania-like good drug effects, stimulation, and talkativeness (Dolder et al. 2017c), and an increase in affective empathy has been reported in bipolar patients during manic episodes (Bodnar and Rybakowski 2017). Additionally, alcohol also enhanced emotional empathy for positive stimuli (Dolder et al. 2017a), similar to D-amphetamine in the present study and indicating that states of greater empathy for positive emotions and prosociality may be induced by various substances and through non-serotonergic/oxytocinergic mechanisms (Bershad et al. 2015). However, additional studies are needed to further clarify the different effects of D-amphetamine and MDMA on empathy and other aspects of social cognition.

The effects of psychoactive substances on sexual arousal have previously been studied using the same SAT for MDMA (Schmid et al. 2014), methylphenidate (Schmid et al. 2014), and alcohol (Dolder et al. 2017a). Specifically, subjects rated explicit sexual images as more pleasant after alcohol administration (Dolder et al. 2017a) and as more exciting after methylphenidate administration compared (Schmid et al. 2014) with placebo or MDMA. MDMA had no effect on sexual arousal on the SAT compared with placebo (Schmid et al. 2014). In the present study, the participants rated explicit sexual images as more pleasant after lisdexamfetamine administration compared with placebo, which is similar to the effects of alcohol on the same test (Dolder et al. 2017a), but the effects of the amphetamines were not content-specific. This means that neutral images (i.e., people or landscapes) were also considered as more attractive after lisdexamfetamine or D-amphetamine administration compared with placebo in the present study. Interestingly, γ-hydroxybutyrate, which is reportedly used to enhance sexual desire, has similarly been shown to induce subjective sexual arousal in response to even sexually neutral pictures (Bosch et al. 2017). These findings should be considered inconclusive and likely depend on the

specific tests that are used and thus need confirmation with other tests. For example, MDMA had no sexually arousing effects on the SAT (Schmid et al. 2015b) but produced sexual arousal-like effects on the Sexual Arousal and Desire Inventory (Dolder et al. 2017b).

Lisdexamfetamine and D-amphetamine had performance-enhancing effects on several of the measures of cognitive performance in the present study. On the DSST, lisdexamfetamine significantly increased the total and correct number of trials completed, indicating an increase in processing speed. D-Amphetamine at 40 mg had no significant effect, in contrast to previously reported increases in performance on the DSST at doses of 10 and 20 mg D-amphetamine (de Wit et al. 2002). Higher plasma concentrations of amphetamine were associated with fewer correct responses on the DSST (Fig. S1), indicating that higher exposure to amphetamine decreased performance within the dose range that was used in the present study. Thus, the 40 mg dose of D-amphetamine may have been too high to improve performance on this test. Considering that lisdexamfetamine increased performance compared with placebo on the group level, the finding of an impaired performance within-group at higher amphetamine concentrations is consistent with an inverted U-shaped dose/concentration–effect relationship.

Neither lisdexamfetamine nor D-amphetamine had an effect on the DS, indicating no changes in working memory capacity, similar to a comparable 0.42 mg/kg D-amphetamine dose (Silber et al. 2006). In contrast, small improvements on the DS were reported after the administration of lower doses of 10 and 20 mg D-amphetamine (de Wit et al. 2002).

On the SST, lisdexamfetamine and D-amphetamine did not alter the Stop-Signal Reaction Time, indicating no change in response inhibition (impulsiveness), but both substances increased accuracy in the "go" trials, consistent with an increase in cognitive performance. Similarly, other studies reported no effects on the Stop-Signal Reaction Time following various doses of D-amphetamine (de Wit et al. 2000, 2002; Fillmore et al. 2005). Effects on the Stop-Signal Reaction Time were only found in a larger, pooled sample ($n = 165$) and in a dose range between 5 and 20 mg D-amphetamine (Weafer and de Wit 2013). However, we found that higher concentrations of amphetamine were associated with lower accuracy and more misses and false alarms on the MCT (Fig. S2–4). Thus, although performance increased in the active medication condition compared with the placebo condition, higher exposure to amphetamine in the amphetamine-treated condition was associated with lower performance, consistent with an inverted U-shaped concentration–effect relationship. The effects of D-amphetamine and dopamine stimulation on cognitive and memory function are known to follow an inverted U-shaped relationship, in which moderate doses and arousal are beneficial to cognition, whereas excessive activation leads to cognitive impairment (Cools and D'Esposito 2011; de Jongh et al. 2008; Robbins and Sahakian 1979; Wood et al. 2014). Additionally, D-amphetamine improved performance more in subjects with poor baseline performance (de Wit et al. 2002) or sleep-deprived subjects (Killgore et al. 2008). Altogether, the cognitive performance findings in the present study are consistent with the view that amphetamines can act as cognitive enhancers in healthy subjects (Franke and Lieb 2010), although the effects were rather small and mainly related to processing speed and vigilance as previously shown (de Jongh et al. 2008; Koelega 1993). The data also confirm and extend the findings of previous studies that evaluated lower doses of D-amphetamine. However, multiple-dose level studies are needed to better describe these dose–effect relationships.

The present study has limitations. First, we only used one dose of each substance. Different doses may have different effects. This view is strongly supported by the finding of an inverse correlation between plasma amphetamine concentrations and performance on the DSST and MCT, despite enhanced performance in these tests in the lisdexamfetamine group and lisdexamfetamine and D-amphetamine groups, respectively, compared with the placebo group and consistent with an inverted U-shaped relationship between amphetamine dose and performance enhancement. Thus, at the group level, we observed enhanced performance by both amphetamines, whereas within treatment groups, performance declined as exposure to the substance increased. This finding indicates that some of the subjects performed worse because the dose was too high, and lower doses of these amphetamines may more effectively or more consistently enhance performance. Second, we did not assess changes in performance over time after drug administration (effect–time curves). A clear strength of the study was the determination of plasma amphetamine concentrations at the time of each test, which allowed us to determine exposure–effect relationships across subjects and evaluate the presence or absence of differences in plasma amphetamine concentrations after lisdexamfetamine and D-amphetamine administration.

In summary, both D-amphetamine and lisdexamfetamine had comparable but only mild effects on aspects of social cognition, including increases in emotional empathy and increased ratings for both sexual and neutral stimuli. It remains to be studied whether these moderate empathogenic and potentially arousing effects alter social perception, interaction, or even risk-associated sexual behavior in subjects using these amphetamines recreationally, as cognitive enhancers, or treatments for ADHD. While reduced recognition of negative emotions under the serotonergic amphetamine-derivative MDMA could be therapeutically useful (Bershad et al. 2016; Hysek et al. 2012, 2014a; Schmid et al. 2014), no such effects on emotion detection could be seen in the present study for the dopaminergic amphetamines.

Both amphetamines similarly enhanced cognitive performance, including test processing speed and response accuracy, compared with placebo in healthy and non-sleep-deprived subjects.

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