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Schmid, Y ; Hysek, Cédric M ; Preller, Katrin H ; Bosch, Oliver G ; Bilderbeck, A C ; Rogers, R D ; Quednow, Boris B ; Liechti, Matthias E

DOI: https://doi.org/10.1016/j.euroneuro.2014.11.020

Effects of methylphenidate and MDMA on appraisal of erotic stimuli and intimate relationships

Short title: methylphenidate, MDMA and sexual arousal

Yasmin Schmid[1], Cédric M. Hysek[1], Katrin H. Preller[2], Oliver G. Bosch[2], Amy C. Bilderbeck[3], Robert D. Rogers[4], Boris B. Quednow[2], Matthias E. Liechti*[,1]

[1]*Psychopharmacology Research, Division of Clinical Pharmacology and Toxicology, Department of Biomedicine and Department of Clinical Research, University Hospital Basel and University of Basel, Switzerland;*

[2]*Experimental and Clinical Pharmacopsychology, Department of Psychiatry, Psychotherapy, and Psychosomatics, Psychiatric Hospital, University of Zurich, Switzerland*

[3]*Department of Psychiatry, Oxford University, UK*

[4]School of Psychology, Bangor University, UK

***Correspondence:** Matthias E. Liechti, Division of Clinical Pharmacology, University Hospital Basel, Hebelstrasse 2, CH-4031 Basel, Switzerland; E-mail: matthias.liechti@usb.ch

Word count: Abstract: 216; Introduction: 698, Discussion: 1644, Manuscript: 4364 words

References: 51

Tables and Figures: Tables: 2; Figures: 2

Trial registration: Clinical trials.gov: http://www.clinicaltrials.gov/ct2/show/NCT01616407

Abstract

Methylphenidate mainly enhances dopamine neurotransmission whereas 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”) mainly enhances serotonin neurotransmission. However, both drugs also induce a weaker increase of cerebral noradrenaline exerting sympathomimetic properties. Dopaminergic psychostimulants are reported to increase sexual drive, while serotonergic drugs typically impair sexual arousal and functions. Additionally, serotonin has also been shown to modulate cognitive perception of romantic relationships. Whether methylphenidate or MDMA alter sexual arousal or cognitive appraisal of intimate relationships is not known. Thus, we evaluated effects of methylphenidate (40mg) and MDMA (75mg) on subjective sexual arousal by viewing erotic pictures and on perception of romantic relationships of unknown couples in a double-blind, randomized, placebo-controlled, crossover study in 30 healthy adults. Methylphenidate, but not MDMA, increased ratings of sexual arousal for explicit sexual stimuli. The participants also sought to increase the presentation time of implicit sexual stimuli by button press after methylphenidate treatment compared with placebo. Plasma levels of testosterone, estrogen, and progesterone were not associated with sexual arousal ratings. Neither MDMA nor methylphenidate altered appraisal of romantic relationships of others. The findings indicate that pharmacological stimulation of dopaminergic but not of serotonergic neurotransmission enhances sexual drive. Whether sexual perception is altered in subjects misusing methylphenidate e.g., for cognitive enhancement or as treatment for attention deficit hyperactivity disorder is of high interest and warrants further investigation.

Keywords: MDMA, methylphenidate, sexual arousal, couples appraisal

Introduction

Methylphenidate is a stimulant drug used for the treatment of attention deficit hyperactivity disorder, but it is also misused as a club drug and a cognitive enhancer (Maier et al., 2013). 3,4-Methylenedioxymethamphetamine (MDMA; "ecstasy") is a popular recreational drug used primarily because of its empathogenic properties, i.e. the drug increases feelings of sociability and closeness to others (Hysek et al., 2013; Morgan et al., 2013). Additionally, both drugs also have psychostimulant properties (Hysek et al., 2014).

It is well recognized that psychoactive substances affect sexual behavior. Users of psychostimulants including cocaine and methamphetamine report increased sexual desire and arousal and enhanced sexual pleasure (Frohmader et al., 2010; Rawson et al., 2002; Semple et al., 2002). In contrast, ecstasy users described inconsistent effects of MDMA on sexual desire (McElrath, 2005; Passie et al., 2005; Theall et al., 2006). Specifically, most users report no desire for penetrative sex but only increased feelings of sensuality, whereas some (in particular gay and bisexual females) use MDMA in particular for sexual enhancement (McElrath, 2005). In another survey, similar proportions of users reported increased or decreased interest in initiating sexual activity while on MDMA (Buffum and Moser, 1986). Additionally, sexual performance seems to be consistently impaired by the drug (Buffum and Moser, 1986; Passie et al., 2005; Zemishlany et al., 2001). Thus, MDMA induces well-being and feelings of closeness to others (Hysek et al., 2013) accompanied by a sensual rather than a sexual enhancement (Passie et al., 2005).

However, research on psychoactive drug use and sexual behavior is typically based on interviews of drug users and has mainly focused on sexual risk taking (McElrath, 2005; Rawson et al., 2002; Semple et al., 2002; Theall et al., 2006). Few studies have objectively evaluated sexual arousal in stimulant drug users (Aguilar de Arcos et al., 2008) or investigated the effects of acute administration of a psychostimulant on sexual perception (Volkow et al., 2007). In particular, intravenous administration of methylphenidate at a high dose of 0.5 mg/kg body weight has been shown to enhance self-reported sexual desire

(Volkow et al., 2007) while administration of a moderate oral dose of methylphenidate (20 mg) had no effects (Volkow et al., 2007). Finally, to our knowledge there are no experimental data on the effects of MDMA on sexual perception and arousal.

Methylphenidate increases dopamine (DA) and norepinephrine (NE) neurotransmission by DA and NA reuptake inhibition (Schmeichel and Berridge, 2013), while MDMA mainly releases serotonin (5-hydroxytryptamine, 5-HT) but also NE (Hysek et al., 2012b). While DA is thought to facilitate sexual drive, 5-HT is stated to inhibit sexual arousal and function (Fabre-Nys, 1998; Frohmader et al., 2010; Melis and Argiolas, 1995; Passie et al., 2005; Pfaus, 2009; Zemishlany et al., 2001). For example, dopaminergic antiparkinson therapy is associated with hypersexuality (Kelley et al., 2012; Uitti et al., 1989; Weintraub et al., 2010) whereas decreased libido and sexual dysfunction are common adverse effects of serotonergic antidepressants (Serretti and Chiesa, 2009). Accordingly, we hypothesized that methylphenidate (40 mg), predominantly enhancing DA, would increase sexual arousal in a Sexual Arousal Task (SAT), while MDMA (75 mg), mainly increasing 5-HT, would not. Because sex hormones may alter sexual arousal (Meston and Frohlich, 2000), we measured testosterone, estrogen, and progesterone plasma levels and explored possible associations with sexual arousal ratings.

Besides from having effects on sexual desire and emotion, psychoactive drugs may also influence aspects of the cognitive appraisal of romantic partnerships. For example, MDMA has been shown to acutely alter related components of social cognition including recognition of facial emotions (Bedi et al., 2010; Hysek et al., 2012a; Hysek et al., 2013; Hysek et al., 2014; Kirkpatrick et al., 2014) and emotional empathy (Hysek et al., 2013; Kuypers et al., 2014; Schmid et al., 2014). Additionally, changes in 5-HT levels may influence cognitions sustaining intimate relationships. Specifically, healthy volunteers perceived photographed couples as being less intimate and romantic after lowering cerebral 5-HT levels by tryptophan depletion (Bilderbeck et al., 2011). In contrast, sub-chronic administration of the selective 5-HT reuptake inhibitor (SSRI) citalopram increased perceived

worth of mutual trust in relationships and reduced importance attributed to physical and intimate aspects of the participants' own relationship (Bilderbeck et al., 2014). We therefore evaluated the effect of a 5-HT releaser (MDMA) and a DA and NA reuptake inhibitor (methylphenidate) on cognitive appraisal of intimate relationships. We hypothesized that MDMA, but not methylphenidate, would increase ratings of intimacy and romance in the Couples Appraisal Task (CAT) (Bilderbeck et al., 2011; Bilderbeck et al., 2014) parallel to its 5-HT enhancing, empathogenic and prosocial effects (Hysek et al., 2013; Kirkpatrick et al., 2014).

Experimental Procedures

Experimental protocol

We used a double-blind, placebo-controlled, cross-over design in 30 subjects each treated with methylphenidate (40mg), MDMA (75 mg), and placebo, resulting in 90 assessments. The order of the three experimental sessions was balanced (Latin Square design), and the washout periods between sessions were at least seven days. The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee and the Swiss Agency for Therapeutic Products (Swissmedic). The study was registered at ClinicalTrials.gov (NCT01616407). All of the subjects provided written informed consent before participating in the study and were paid for their participation.

Participants

Thirty healthy subjects (15 men, 15 women) with a mean age of 24 ± 4.2 years (mean ± SD; range 18 to 32 years) were recruited from the University of Basel. All subjects were self-reported heterosexuals. Inclusion criteria were age 18 to 45 years and body mass index 18 to 27 kg/m^2. The exclusion criteria were a history of psychiatric disorders (determined by the

Structured Clinical Interview for Axis I and II Disorders according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition) or chronic or acute physical illness (assessed by physical examination, electrocardiogram, standard hematology, and chemical blood analysis). Additional exclusion criteria were pregnancy, tobacco smoking (>10 cigarettes/day), a lifetime history of using illicit drugs more than five times, with the exception of past cannabis use, and any illicit drug use including cannabis within the last two months or during the study period, determined by urine tests conducted during screening and before the test sessions using TRIAGE 8 (Biosite, San Diego, California). Twenty-two subjects were "ecstasy"/MDMA-naive. Eight subjects had used MDMA less than five times. One subject reported previous single use of methylphenidate as cognitive enhancer. Six female participants used hormonal contraception. The female subjects who did not use hormonal contraception were investigated during the follicular phase (day 2 to 14).

Study drugs

±MDMA hydrochloride (Lipomed AG, Arlesheim, Switzerland) was prepared as gelatin capsules with mannitol as filler. Identical placebo (only mannitol) capsules were prepared. MDMA was administered in a single absolute dose of 75 mg corresponding to 1.1 ± 0.13 mg/kg body weight (range 0.8-1.3 mg/kg body weight). This dose of MDMA corresponds to that typically found in a single ecstasy pill (Brunt et al., 2012). Immediate-release methylphenidate tablets (4×10 mg, Ritalin, Novartis AG, Bern, Switzerland) were encapsulated within opaque gelatin capsules (with mannitol as filler), and identical placebo capsules (mannitol pill plus mannitol filler) were prepared. This is a typical and well-tolerated clinical and research dose of methylphenidate (Korostenskaja et al., 2008) producing similar cardiovascular stimulation to the dose of MDMA used (Schmid et al., 2014).

Study procedures

The experimental sessions took place in a quiet hospital research ward with no more than two research subjects of the same sex present per session. Before the first session, subjects completed a brief training to get familiarized with the computer tasks. Drug administration was at 10:00 AM. The SAT and CAT were performed at 150 and 170 minutes after drug administration, respectively, when maximal plasma levels of the drugs were expected (Hysek et al., 2014). The actual times to peak concentration were (mean±SD) 153±50 and 130±48 min after MDMA and methylphenidate administration, respectively, as reported together with the concentration-time curves (Schmid et al., 2014). A standardised small lunch was served at 13:30 PM. Subjects were sent home at 4:30 PM. During the day, subjective effects, vital signs and adverse drug effects were assessed as reported elsewhere (Schmid et al., 2014). Additional test of emotion recognition and empathy were performed 75-105 min after drug administration as reported elsewhere (Schmid et al., 2014).

Measures

Sexual Arousal Task

The SAT included 16 colour photographs taken 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 persons without sexual signals. Erotic pictures included four implicit sexual scenes (i.e., no primary or secondary sexual organs are shown explicitly but persons were shown in stimulating poses showing some skin) and four explicit sexual scenes (i.e., clearly pornographic poses or scenes). In the neutral (persons), implicit and explicit condition, two pictures with single persons and two pictures with couples were shown, respectively. Thus, we had four pictures of neutral objects (two) and landscapes (two), four pictures of neutral persons (two singles and two couples), four pictures of implicit sexual scenes (two singles and two couples), and four pictures of explicit erotic scenes (two singles and two couples). Additionally, there was a male and a female version of the test: female subjects were only shown males in the single person condition, while male subjects received

only female single person stimuli. Because men and women were tested on different tasks, scores cannot be compared directly. The SAT included two subtasks, an “effort task” and an “arousal rating task”. In the effort task, pictures were shown for one sec. To prolong the presentation, participants were instructed to click rapidly on the keyboard for as long as they wanted to see the picture. One or more clicks per sec resulted in a prolongation of the presentation by another sec until no more clicks occurred within one sec. Outcome measures were the total number of clicks and the resulting duration the picture was presented. In the arousal rating task, participants were asked to rate each picture on 5 dimensions. The dimensions included “pleasant”, “arousing/exciting”, “attractive”, “likeable”, and “erotic”. The original Self-Assessment Manikin were 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 performed on a 9-point rating scale marked “not at all” on the left and “very” on the right end. Ratings of all neutral, implicit sexual or explicit sexual pictures were averaged for each dimension. The SAT was implemented in Presentation Version 14.8 (Neurobehavioral Systems, Albany, CA, USA) and shown on a computer screen.

Couples Appraisal Task

To assess the appraisal of intimate relationships we used a German adaptation of the previously described CAT (Bilderbeck et al., 2011; Bilderbeck et al., 2014). Briefly, 18 photographs of heterosexual couples in genuine relationships were presented on a computer screen. All facial expressions were broadly neutral. Nine couples showed physical contact such as affiliative or romantic gestures and nine couples were standing apart and were not touching each other. Touching and non-touching couples were randomly mixed. Participants rated each couple using visual analogue scales (0-10) with “not at all” and “very” as anchor points for the following descriptors, which were selected to display subjects’ perceived ratings of relationship stability (Bilderbeck et al., 2011; Bilderbeck et al., 2014): “intimate”, “romantic”, “supportive”, “trusting”, “conflict resolution”, “enduring”, and “good physical

relationship". Ratings of "turbulence" and "bickering" were used as negative relationship characteristics. Additionally, "dominance" and "balance of love" were rated using scales labelled with "man" on the left and "woman" on the right, with "neutral" at the midpoint. Participants' ratings for each of the descriptors were then averaged over touching and non-touching couples. The CAT was also implemented in Presentation Version 14.8 (Neurobehavioral Systems, Albany, CA, USA).

Endocrine measures

Plasma levels of testosterone (men and women), estradiol and progesterone (only women) were measured at baseline and 2 h after drug administration using commercial electro-chemiluminescence immunoassays (Cobas ®, Roche Diagnostics, Basel, Switzerland).

Data analysis

Statistical analysis was performed using Statistica 12 (StatSoft, Tulsa, OK, USA). SAT data were analysed using analyses of variance (ANOVAs) with drug (methylphenidate, MDMA, placebo) and sexual content (neutral, implicit, explicit) as within-subject factors. Drug effects on ratings of couples in the CAT were similarly analysed using ANOVAs with drug and touching (touching vs. non-touching) as within-subject factor. ANOVAs were also used to compare hormone levels (differences from baseline, ΔE_{max}). Tukey post hoc were performed based on significant main effects or interactions. Sex-differences were assessed with sex added to the ANOVAs as between-subject factor for each descriptor. Additional ANOVAs were performed with drug order to exclude carry-over effects. Spearman's rank correlations were used to determine associations between measures. Differences associated with p-values lower than 0.05 (two-tailed) were considered statistically significant.

Results

Sexual Arousal Task

Data from two women and two men were missing for the SAT effort task and for two women for the SAT arousal task due to technical problems. Effects of methylphenidate and MDMA on SAT scores are shown in Table 1 and Figure 1.

In the effort subtask, there were significant drug × sexual content interactions for both the number of clicks and the duration of the presentation [$F(4,100)=2.6$; $p<0.05$ and $F(4,100)=3.0$, $p<0.05$; respectively]. There was a significant main effect of sexual content (neutral, implicit, explicit) on both the number of clicks [$F(2,50)=18.3$; $p<0.001$] and on the duration of the presentation [$F(2,50)=22.2$; $p<0.001$]. The total number of clicks was lower for explicit compared with implicit and neutral stimuli (both $p<0.001$). Both, methylphenidate and MDMA increased the number of clicks for implicit sexual stimuli compared with placebo ($p<0.001$ and $p<0.01$, respectively). Only methylphenidate also significantly increased the presentation time for the sexual implicit stimuli compared with placebo ($p<0.05$).

In the arousal subtask, there were significant main effects of sexual content (neutral, implicit, explicit) for all ratings [all $F(2,54)>50$; $p<0.001$]. Implicit sexual content increased ratings on all dimensions compared with neutral contents (all $p<0.001$, Table 1) and ratings were also mostly higher compared with explicit sexual contents (most $p<0.001$). Explicit sexual content also increased ratings of arousal/excitement, attractiveness, and erotic. There was a significant drug × sexual content interaction on ratings of “arousing/exciting” [$F(4,108) = 3.59$; $p<0.01$]. Methylphenidate significantly increased ratings of arousal/excitement compared with placebo ($p<0.01$) or MDMA ($p<0.001$) for pictures with an explicit sexual content. Methylphenidate similarly tended to increase ratings of erotic compared with placebo and MDMA [$F(4,108) = 2.17$; $p=0.08$; both post hoc tests: $p<0.05$] (Table 1). MDMA did not alter any ratings compared with placebo. The findings remained largely the same when an analysis was altered to include, for the neutral condition, only the pictures displaying persons (i.e. excluding landscape and object pictures). Finally, introducing the additional factor “number of shown persons” (singles vs. couples) did also not change the results and the

factor itself was also not significant. Surprisingly, there were no significant differences between male or female participants in any of the ratings or drug effects.

Couples Appraisal Task

Drug effects in the CAT are shown in Figure 2. There were no drug effects on any of the descriptors in the CAT, indicating that neither methylphenidate nor MDMA altered appraisal of intimate relationship. In line with previous studies (Bilderbeck et al., 2011; Bilderbeck et al., 2014), ratings of all relationship stability descriptors ("intimate", "romantic", "supportive", "trusting", "conflict resolution", "enduring", and "good physical relationship") were significantly increased for touching couples compared with couples who were standing apart [$F(1.28)>10$; $p<0.01$ for all descriptors]. Again, no sex differences or sex × drug interactions were observed.

Endocrine measures

Drug effects on plasma levels of testosterone, estradiol, and progesterone are shown in Table 2. There were no significant correlations between plasma sex hormone levels and sexual arousal ratings after any of the drugs (drug-induced changes or change scores [$\Delta_{placebo\text{-}drug}$]). There was a significant main effect of drug on testosterone in women [$F(2,28)=5.392$; $p<0.02$] with slightly higher levels after methylphenidate compared with placebo ($p<0.05$). Additionally, there was a significant main effect of drug on estradiol [$F(2,28)=4.672$; $p<0.02$], with higher levels after methylphenidate compared with MDMA ($p<0.05$).

Discussion

The present experimental study showed that healthy adults rated pictures with an explicit sexual content as more exciting after acute administration of methylphenidate compared with placebo or MDMA. Concurrently, methylphenidate increased the number of

responses (button presses) performed by the participants in order to prolong the presentation of images with an implicit sexual content and the actual presentation duration of these pictures. In contrast, MDMA had no effect on subjective arousal ratings of erotic pictures with implicit or explicit sexual content. However, similar to methylphenidate, MDMA also increased the number of responses for implicit sexual stimuli but the invested effort was too small to significantly prolong the presentation time. Surprisingly, none of the drugs altered appraisal of romantic relationships in a task previously shown to be sensitive to alterations in the 5-HT system (Bilderbeck et al., 2011; Bilderbeck et al., 2014).

Psychostimulants are believed to acutely increase sexual arousal and drive, but such effects have rarely been evaluated using actual tests and in controlled settings. Consistent with our findings, methylphenidate has previously been shown to increase self-reports of sexual desire (Volkow et al., 2007). However, the effect of methylphenidate on sexual desire was observed only after intravenous administration of methylphenidate but not after oral administration of a moderate dose of 20 mg (Volkow et al., 2007). Additionally, subjects rated their sexual desire in the absence of any sexual stimuli and while lying in a tomograph (Volkow et al., 2007). In contrast, in our study, subjects were viewing pictures with implicit and explicit sexual content and we evaluated drug effects on subjective sexual arousal elicited by these visual sexual stimuli. Moreover, we administered a higher dose of methylphenidate (40 mg), which might lead to similar plasma levels as intravenous administration of a lower dose (20 mg) in the study of Volkow and colleagues (Volkow et al., 2007). Consistent with the present findings, other stimulants with similar dopaminergic action including cocaine and methamphetamine have been subjectively reported to increase sex drive as well (Rawson et al., 2002) and are commonly linked with risk-associated sexual behaviours (Frohmader et al., 2010; Rawson et al., 2002). Furthermore, abstinent cocaine users also rated explicit erotic pictures from the IAPS as more pleasant compared with users of alcohol or heroin (Aguilar de Arcos et al., 2008).

The mechanisms underlying increased sexual arousal following administration of psychoactive substances have only partly been elucidated. It has been proposed that DA is responsible for the increase in sexual arousal following administration of methylphenidate or methamphetamine by disrupting conditioned inhibition of sexual arousal and behaviour (Volkow et al., 2007) although these drugs also enhance NE in addition to DA.

MDMA did not enhance subjective sexual arousal ratings in response to visual stimuli in the present study. However, MDMA, similar to methylphenidate, significantly increased the number of clicks to potentially prolong the presentation of the implicit but not of the explicit sexual stimuli compared with placebo. Viewing implicit erotic pictures was rated as more pleasant compared with viewing explicit pornographic pictures in all drug conditions. Thus, MDMA increased responding only for erotic stimuli that were more pleasant to view. Interviews of recreational MDMA users documented that most respondents reported feelings of emotional closeness while consuming MDMA but without the desire for penetrative sex (McElrath, 2005). However, other respondents reported that MDMA increased their sexual arousal and some (in particular gay and bisexual females) had used MDMA specifically for sexual enhancement (McElrath, 2005). Another interview study found that ecstasy use seemed to increase sexual desire but not the ability to achieve an erection or orgasm (Theall et al., 2006; Zemishlany et al., 2001). Thus, MDMA mainly seems to enhance pleasure in touching and physical closeness rather than actual sexual engagement and is also reported to impair sexual performance (Frohmader et al., 2010; Passie et al., 2005; Theall et al., 2006; Zemishlany et al., 2001). Neurochemically, MDMA enhances 5-HT and NE and weakly also DA transmission (Hysek et al., 2012b) but additionally, MDMA also releases oxytocin and prolactin (Hysek et al., 2012a; Hysek et al., 2013). Dopamine, NE and oxytocin enhance and 5-HT and prolactin inhibit sexual excitation (Kruger et al., 2005; Pfaus, 2009). Sexual dysfunction associated with serotonergic drugs has been shown to involve 5-HT_{1B}, 5-HT_2 and 5-HT_3 receptors (Fabre-Nys, 1998; Meston and Frohlich, 2000). In addition to releasing 5-HT and NE (Hysek et al., 2012b), MDMA also directly binds to serotonergic 5-HT_{2A}-, 5-HT_{2B}-, and 5-HT_{2C}-receptors (Simmler et al., 2013; Teitler et al., 1990). It is likely that the

serotonergic effects predominate in this neurochemical cocktail, resulting in the absence of sexually enhancing or even presence of impairing effects for MDMA at the doses typically used by humans.

Sexual stimuli and behaviour activate the mesolimbic DA reward system similarly to other rewarding/pleasant stimuli or drugs of abuse (Georgiadis and Kringelbach, 2012; Holstege et al., 2003). Our study findings are consistent with the role for DA in sexual arousal because methylphenidate increased sexual arousal and MDMA did not. In the case of MDMA, the additional release of NE may have had some small sexually enhancing effects, which were masked by concomitant 5-HT release, which is known to dampen sexual function (Pfaus, 2009). Consistent with our finding of increased sexual arousal after methylphenidate, the DA precursor levodopa enhanced the activation of the nucleus accumbens when subliminal sexual stimuli were shown, whereas the DA D_2-receptor antagonist haloperidol decreased activations (Oei et al., 2012). Accordingly, the DA and NE transporter inhibitor and antidepressant bupropion, which has less side effects on sexual arousal and libido than serotonergic antidepressants, increased activation of brain regions related to sexual functioning (Abler et al., 2011). Moreover, flibanserin, which enhances NE and DA while reducing 5-HT (Borsini et al., 2002), increased sexual desire in women with hypoactive sexual desire (Katz et al., 2013). Finally, dextroamphetamine and methylphenidate have been reported to reverse the sexually impairing effects of 5-HT transporter blockers and to even enhance sexual arousal and function in female and male patients with depression (Bartlik et al., 1995).

Although MDMA did not enhance sexual arousal in the present study, it appears to induce effects that may affect sexual interaction. In particular, MDMA increased feelings of closeness to others and sociability and alters sensual perception including touch (Hysek et al., 2013; Liechti et al., 2001; Schmid et al., 2014). Despite these emotional changes, MDMA did not alter the appraisal of romantic partnerships of others in the present study contrary to our expectation. It has previously been shown that presumably enhancing 5-HT tone with

citalopram across eight days increased ratings of trusting in the CAT and reduced the importance of physical and intimate aspects of the participant's own relationships (Bilderbeck et al., 2014). Contrarily, lowering cerebral 5-HT by tryptophan depletion has changed ratings of relationship characteristics of photographed couples, including decreased intimacy and romance (Bilderbeck et al., 2014). Alterations in 5-HT levels did not only influence relationship characteristic ratings but also ratings of dominance with women providing higher ratings of male dominance after 5-HT reduction (Bilderbeck et al., 2011), and decreased ratings of turbulence and bickering in men after citalopram (Bilderbeck et al., 2014). However, MDMA was administered acutely while citalopram was administered chronically probably resulting in adaptive changes to the 5-HT system (Stahl, 1998). Additionally, MDMA is also less selective for the 5-HT system than citalopram (see above). Moreover, although MDMA stimulates 5-HT release much more than citalopram, it did not alter ratings of general relationship stability or indices of dominance and discord in the CAT. Thus, we might have "overstimulated" our participants as – similar to DA and NE neurotransmission – an inverted U-shaped function has also been postulated for the 5-HT system (Roiser et al., 2006). Interestingly, MDMA produced subjective feelings of trust and openness towards others (Schmid et al., 2014), thus producing effects that were very similar to those perceived important in others after citalopram administration (Bilderbeck et al., 2014).

While pathologically low levels of testosterone result in decreased sexual interest and activity, variability in the normal/upper range is generally not considered to influence sexual interest or behavior in men (Meston and Frohlich, 2000). Similarly, estrogen and progesterone play only a minimal role in female sexual desire (Meston and Frohlich, 2000). We found that plasma levels of testosterone, estrogen, or progesterone were not associated with sexual arousal ratings in the present study. Consistently, different estrogen and progesterone levels exerted only minor effects on neural responses to explicit visual erotic stimulation in women (Abler et al., 2013).

The present study has several limitations. First, we used only single doses of MDMA and methylphenidate. However, the used doses of both drugs that produced similar cardiovascular stimulation (Schmid et al., 2014), indicating equipotent stimulant effects. Nevertheless, dose-response relationships are lacking as in most of such human neuropsychopharmacological experiments. As an important strength, we included two active drugs into the design allowing for comparisons of each active drug with both the placebo and another active drug condition. Second, only acute drug effects were assessed and the impact of chronic use of methylphenidate or MDMA on the present measures remains unknown. Third, sexual stimuli were presented without time limit. It has previously been shown that exposure to supraliminal sexual images showed activation in both arousal- but also control-related brain areas (Gillath and Canterberry, 2012). Men presumably show higher sexual drive (Baumeister et al., 2001), but may also exhibit stronger urge to control it when being consciously aroused, therefore resulting in similar arousal ratings than women. Future studies will have to examine drug-effects on subliminal exposure to sexual stimuli.

In summary, methylphenidate but not MDMA increased ratings of sexual excitation by visual stimuli with explicit sexual content but participants responded more to implicit stimuli after both drugs. Neither MDMA nor methylphenidate altered appraisal of romantic relationships of others. The findings are consistent with a role of DA in sexual drive. It remains to be studied whether sexual perception or even risk-associated sexual behavior is altered in subjects using methylphenidate chronically as a recreational drug, for cognitive enhancement, or as treatment for attention deficit hyperactivity disorder.

References

Abler, B., Kumpfmuller, D., Gron, G., Walter, M., Stingl, J., Seeringer, A., 2013. Neural correlates of erotic stimulation under different levels of female sexual hormones. PloS one 8, e54447.

Abler, B., Seeringer, A., Hartmann, A., Gron, G., Metzger, C., Walter, M., Stingl, J., 2011. Neural correlates of antidepressant-related sexual dysfunction: a placebo-controlled fMRI study on healthy males under subchronic paroxetine and bupropion. Neuropsychopharmacology 36, 1837-1847.

Aguilar de Arcos, F., Verdejo-Garcia, A., Lopez Jimenez, A., Montanez Pareja, M., Gomez Juarez, E., Arraez Sanchez, F., Perez Garcia, M., 2008. Changes in emotional response to visual stimuli with sexual content in drug abusers. Adicciones 20, 117-124.

Bartlik, B.D., Kaplan, P., Kaplan, H.S., 1995. Psychostimulants apparently reverse sexual dysfunction secondary to selective serotonin re-uptake inhibitors. J Sex Marital Ther 21, 264-271.

Baumeister, R.F., Catanese, K.R., Vohs, K.D., 2001. Is there a gender difference in strength of sex drive? Theoretical views, conceptual distinctions, and a review of relevant evidence. . Pers Soc Psychol Rev 5, 242-273.

Bedi, G., Hyman, D., de Wit, H., 2010. Is ecstasy an "empathogen"? Effects of ± 3,4-methylenedioxymethamphetamine on prosocial feelings and identification of emotional states in others. Biol Psychiatry 68, 1134-1140.

Bilderbeck, A.C., McCabe, C., Wakeley, J., McGlone, F., Harris, T., Cowen, P.J., Rogers, R.D., 2011. Serotonergic activity influences the cognitive appraisal of close intimate relationships in healthy adults. Biol Psychiatry 69, 720-725.

Bilderbeck, A.C., Wakeley, J., Godlewska, B.R., McGlone, F., Harris, T., Cowen, P.J., Rogers, R.D., 2014. Preliminary evidence that sub-chronic citalopram triggers the re-

evaluation of value in intimate partnerships. Social cognitive and affective neuroscience 9, 1419-1425.

Borsini, F., Evans, K., Jason, K., Rohde, F., Alexander, B., Pollentier, S., 2002. Pharmacology of flibanserin. CNS Drug Rev 8, 117-142.

Bradley, M.M., Lang, P.J., 1994. Measuring emotion: the self-assessment manikin and the semantic differential. J Behav Ther Exp Psychiatry 25, 49-59.

Brunt, T.M., Koeter, M.W., Niesink, R.J., van den Brink, W., 2012. Linking the pharmacological content of ecstasy tablets to the subjective experiences of drug users. Psychopharmacology (Berl) 220, 751-762.

Buffum, J., Moser, C., 1986. MDMA and human sexual function. J Psychoactive Drugs 18, 355-359.

Fabre-Nys, C., 1998. Steroid control of monoamines in relation to sexual behaviour. Rev Reprod 3, 31-41.

Frohmader, K.S., Pitchers, K.K., Balfour, M.E., Coolen, L.M., 2010. Mixing pleasures: review of the effects of drugs on sex behavior in humans and animal models. Horm Behav 58, 149-162.

Georgiadis, J.R., Kringelbach, M.L., 2012. The human sexual response cycle: brain imaging evidence linking sex to other pleasures. Prog Neurobiol 98, 49-81.

Gillath, O., Canterberry, M., 2012. Neural correlates of exposure to subliminal and supraliminal sexual cues. Social cognitive and affective neuroscience 7, 924-936.

Holstege, G., Georgiadis, J.R., Paans, A.M., Meiners, L.C., van der Graaf, F.H., Reinders, A.A., 2003. Brain activation during human male ejaculation. J Neurosci 23, 9185-9193.

Hysek, C.M., Domes, G., Liechti, M.E., 2012a. MDMA enhances "mind reading" of positive emotions and impairs "mind reading" of negative emotions. Psychopharmacology (Berl) 222, 293-302.

Hysek, C.M., Schmid, Y., Simmler, L.D., Domes, G., Heinrichs, M., Eisenegger, C., Preller, K.H., Quednow, B.B., Liechti, M.E., 2013. MDMA enhances emotional empathy and prosocial behavior. Social cognitive and affective neuroscience. doi: 10.1093/scan/nst161.

Hysek, C.M., Simmler, L.D., Nicola, V., Vischer, N., Donzelli, M., Krähenbühl, S., Grouzmann, E., Hoener, M.C., Liechti, M.E., 2012b. Duloxetine inhibits effects of MDMA ("ecstasy") in vitro and in humans in a randomized placebo-controlled laboratory study. PloS one 7, e36476.

Hysek, C.M., Simmler, L.D., Schillinger, N., Meyer, N., Schmid, Y., Donzelli, M., Grouzmann, E., Liechti, M.E., 2014. Pharmacokinetic and pharmacodynamic effects of methylphenidate and MDMA administered alone and in combination. Int J Neuropsychopharmacol 17, 371-381.

Katz, M., DeRogatis, L.R., Ackerman, R., Hedges, P., Lesko, L., Garcia, M., Jr., Sand, M., investigators, B.t., 2013. Efficacy of flibanserin in women with hypoactive sexual desire disorder: results from the BEGONIA trial. J Sex Med 10, 1807-1815.

Kelley, B.J., Duker, A.P., Chiu, P., 2012. Dopamine agonists and pathologic behaviors. Parkinsons Dis 2012, 603631.

Kirkpatrick, M.G., Lee, R., Wardle, M.C., Jacob, S., de Wit, H., 2014. Effects of MDMA and intranasal oxytocin on social and emotional processing. Neuropsychopharmacology 39, 1654-1663.

Korostenskaja, M., Kicic, D., Kahkonen, S., 2008. The effect of methylphenidate on auditory information processing in healthy volunteers: a combined EEG/MEG study. Psychopharmacology (Berl) 197, 475-486.

Kruger, T.H., Hartmann, U., Schedlowski, M., 2005. Prolactinergic and dopaminergic mechanisms underlying sexual arousal and orgasm in humans. World J Urol 23, 130-138.

Kuypers, K.P., de la Torre, R., Farre, M., Yubero-Lahoz, S., Dziobek, I., Van den Bos, W., Ramaekers, J.G., 2014. No evidence that MDMA-induced enhancement of emotional empathy is related to peripheral oxytocin levels or 5-HT_{1a} receptor activation. PloS one 9, e100719.

Lang, P.J., Bradley, M.M., Cuthbert, B.N., 2008. International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual. University of Florida, Gainesville, FL.

Liechti, M.E., Gamma, A., Vollenweider, F.X., 2001. Gender differences in the subjective effects of MDMA. Psychopharmacology (Berl) 154, 161-168.

Maier, L.J., Liechti, M.E., Herzig, F., Schaub, M.P., 2013. To dope or not to dope: neuroenhancement with prescription drugs and drugs of abuse among Swiss university students. PloS one 8, e77967.

McElrath, K., 2005. MDMA and sexual behavior: ecstasy users' perceptions about sexuality and sexual risk. Subst Use Misuse 40, 1461-1477.

Melis, M.R., Argiolas, A., 1995. Dopamine and sexual behavior. Neurosci Biobehav Rev 19, 19-38.

Meston, C.M., Frohlich, P.F., 2000. The neurobiology of sexual function. Arch Gen Psychiatry 57, 1012-1030.

Morgan, C.J., Noronha, L.A., Muetzelfeldt, M., Fielding, A., Curran, H.V., 2013. Harms and benefits associated with psychoactive drugs: findings of an international survey of active drug users. J Psychopharmacol 27, 497-506.

Oei, N.Y., Rombouts, S.A., Soeter, R.P., van Gerven, J.M., Both, S., 2012. Dopamine modulates reward system activity during subconscious processing of sexual stimuli. Neuropsychopharmacology 37, 1729-1737.

Passie, T., Hartmann, U., Schneider, U., Emrich, H.M., Kruger, T.H., 2005. Ecstasy (MDMA) mimics the post-orgasmic state: impairment of sexual drive and function during acute MDMA-effects may be due to increased prolactin secretion. Med Hypotheses 64, 899-903.

Pfaus, J.G., 2009. Pathways of sexual desire. J Sex Med 6, 1506-1533.

Rawson, R.A., Washton, A., Domier, C.P., Reiber, C., 2002. Drugs and sexual effects: role of drug type and gender. J Subst Abuse Treat 22, 103-108.

Roiser, J.P., Blackwell, A.D., Cools, R., Clark, L., Rubinsztein, D.C., Robbins, T.W., Sahakian, B.J., 2006. Serotonin transporter polymorphism mediates vulnerability to loss of incentive motivation following acute tryptophan depletion. Neuropsychopharmacology 31, 2264-2272.

Schmeichel, B.E., Berridge, C.W., 2013. Neurocircuitry underlying the preferential sensitivity of prefrontal catecholamines to low-dose psychostimulants. Neuropsychopharmacology 38, 1079-1084.

Schmid, Y., Hysek, C.M., Simmler, L.D., Crockett, M.J., Quednow, B.B., Liechti, M.E., 2014. Differential effects of MDMA and methylphenidate on social cognition. J Psychopharmacol 28, 847-856.

Semple, S.J., Patterson, T.L., Grant, I., 2002. Motivations associated with methamphetamine use among HIV+ men who have sex with men. J Subst Abuse Treat 22, 149-156.

Serretti, A., Chiesa, A., 2009. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychopharmacol 29, 259-266.

Simmler, L., Buser, T., Donzelli, M., Schramm, Y., Dieu, L.H., Huwyler, J., Chaboz, S., Hoener, M., Liechti, M.E., 2013. Pharmacological characterization of designer cathinones in vitro. Br J Pharmacol 168, 458-470.

Stahl, S.M., 1998. Mechanism of action of serotonin selective reuptake inhibitors. Serotonin receptors and pathways mediate therapeutic effects and side effects. J Affect Disord 51, 215-235.

Teitler, M., Leonhardt, S., Appel, N.M., De Souza, E.B., Glennon, R.A., 1990. Receptor pharmacology of MDMA and related hallucinogens. Ann N Y Acad Sci 600, 626-638; discussion 638-629.

Theall, K.P., Elifson, K.W., Sterk, C.E., 2006. Sex, touch, and HIV risk among ecstasy users. AIDS Behav 10, 169-178.

Uitti, R.J., Tanner, C.M., Rajput, A.H., Goetz, C.G., Klawans, H.L., Thiessen, B., 1989. Hypersexuality with antiparkinsonian therapy. Clin Neuropharmacol 12, 375-383.

Volkow, N.D., Wang, G.J., Fowler, J.S., Telang, F., Jayne, M., Wong, C., 2007. Stimulant-induced enhanced sexual desire as a potential contributing factor in HIV transmission. Am J Psychiatry 164, 157-160.

Weintraub, D., Koester, J., Potenza, M.N., Siderowf, A.D., Stacy, M., Voon, V., Whetteckey, J., Wunderlich, G.R., Lang, A.E., 2010. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol 67, 589-595.

Zemishlany, Z., Aizenberg, D., Weizman, A., 2001. Subjective effects of MDMA ('Ecstasy') on human sexual function. Eur Psychiatry 16, 127-130.

Figure 1. In the Sexual Arousal Task, pictures with sexual implicit or explicit content were rated significantly more “arousing/exciting” than neutral pictures (both $p<0.001$). Methylphenidate significantly increased ratings of “arousing/exciting” for pictures with an explicit sexual content compared with placebo ($p<0.01$) or MDMA ($p<0.001$). Data are expressed as mean ± SEM in 28 participants. **$p < 0.01$ and ***$p < 0.001$ for significant differences. Pla, placebo; MPH, methylphenidate; MDMA, 3,4-methylenedioxymethamphetamine.

Figure 2. In the Couples Appraisal Task, neither methylphenidate nor MDMA altered appraisal of intimate relationships compared with placebo. Data are expressed as mean ± SEM in 30 participants. MDMA, 3,4-methylenedioxymethamphetamine.

Effects of methylphenidate and MDMA on appraisal of erotic stimuli and intimate relationships

Short title: methylphenidate, MDMA and sexual arousal

Yasmin Schmid[1], Cédric M. Hysek[1], Katrin H. Preller[2], Oliver G. Bosch[2], Amy C. Bilderbeck[3], Robert D. Rogers[4], Boris B. Quednow[2], Matthias E. Liechti*[,1]

[1]*Psychopharmacology Research, Division of Clinical Pharmacology and Toxicology, Department of Biomedicine and Department of Clinical Research, University Hospital Basel and University of Basel, Switzerland;*

[2]*Experimental and Clinical Pharmacopsychology, Department of Psychiatry, Psychotherapy, and Psychosomatics, Psychiatric Hospital, University of Zurich, Switzerland*

[3]*Department of Psychiatry, Oxford University, UK*

[4]School of Psychology, Bangor University, UK

***Correspondence:** Matthias E. Liechti, Division of Clinical Pharmacology, University Hospital Basel, Hebelstrasse 2, CH-4031 Basel, Switzerland; E-mail: matthias.liechti@usb.ch

Word count: Abstract: 216; Introduction: 698, Discussion: 1644, Manuscript: 4364~~175~~ words

References: ~~50~~51

Tables and Figures: Tables: 2; Figures: 2

Trial registration: Clinical trials.gov: http://www.clinicaltrials.gov/ct2/show/NCT01616407

Abstract

Methylphenidate mainly enhances dopamine neurotransmission whereas 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”) mainly enhances serotonin neurotransmission. However, both drugs also induce a weaker increase of cerebral noradrenaline exerting sympathomimetic properties. Dopaminergic psychostimulants are reported to increase sexual drive, while serotonergic drugs typically impair sexual arousal and functions. Additionally, serotonin has also been shown to modulate cognitive perception of romantic relationships. Whether methylphenidate or MDMA alter sexual arousal or cognitive appraisal of intimate relationships is not known. Thus, we evaluated effects of methylphenidate (40mg) and MDMA (75mg) on subjective sexual arousal by viewing erotic pictures and on perception of romantic relationships of unknown couples in a double-blind, randomized, placebo-controlled, crossover study in 30 healthy adults. Methylphenidate, but not MDMA, increased ratings of sexual arousal for explicit sexual stimuli. The participants also sought to increase the presentation time of implicit sexual stimuli by button press after methylphenidate treatment compared with placebo. Plasma levels of testosterone, estrogen, and progesterone were not associated with sexual arousal ratings. Neither MDMA nor methylphenidate altered appraisal of romantic relationships of others. The findings indicate that pharmacological stimulation of dopaminergic but not of serotonergic neurotransmission enhances sexual drive. Whether sexual perception is altered in subjects misusing methylphenidate e.g., for cognitive enhancement or as treatment for attention deficit hyperactivity disorder is of high interest and warrants further investigation.

Keywords: MDMA, methylphenidate, sexual arousal, couples appraisal

Introduction

Methylphenidate is a stimulant drug used for the treatment of attention deficit hyperactivity disorder, but it is also misused as a club drug and a cognitive enhancer (Maier et al., 2013). 3,4-Methylenedioxymethamphetamine (MDMA; "ecstasy") is a popular recreational drug used primarily because of its empathogenic properties, i.e. the drug increases feelings of sociability and closeness to others (Hysek et al., 2013; Morgan et al., 2013). Additionally, both drugs also have psychostimulant properties (Hysek et al., 2014).

It is well recognized that psychoactive substances affect sexual behavior. Users of ~~Many~~ psychostimulants including cocaine and methamphetamine report increased ~~subjective reports of~~ sexual desire and arousal and enhanced ~~to enhance~~ sexual pleasure (Frohmader et al., 2010; Rawson et al., 2002; Semple et al., 2002). In contrast, ecstasy users described inconsistent effects of MDMA on sexual desire (McElrath, 2005; Passie et al., 2005; Theall et al., 2006). Specifically, most users report no desire for penetrative sex but only increased feelings of sensuality, whereas some (in particular gay and bisexual females) use MDMA in particular for sexual enhancement (McElrath, 2005). In another survey, similar proportions of users reported increased or decreased interest in initiating sexual activity while on MDMA (Buffum and Moser, 1986). ~~, while~~ Additionally, sexual performance seems to be consistently impaired by the drug (Buffum and Moser, 1986; Passie et al., 2005; Zemishlany et al., 2001). Thus, MDMA induces well-being and feelings of closeness to others (Hysek et al., 2013) accompanied by a sensual rather than a sexual enhancement (Passie et al., 2005).

However, research on psychoactive drug use and sexual behavior is typically based on interviews of drug users and has mainly focused on sexual risk taking (McElrath, 2005; Rawson et al., 2002; Semple et al., 2002; Theall et al., 2006). Few studies have objectively evaluated sexual arousal in stimulant drug users (Aguilar de Arcos et al., 2008) or investigated the effects of acute administration of a psychostimulant on sexual perception (Volkow et al., 2007). In particular, intravenous administration of methylphenidate at a high dose of 0.5 mg/kg body weight has been shown to enhance self-reported sexual desire

(Volkow et al., 2007) while administration of a moderate oral dose of methylphenidate (20 mg) had no effects (Volkow et al., 2007). Finally, to our knowledge there are no experimental data on the effects of MDMA on sexual perception and arousal.

Methylphenidate increases dopamine (DA) and norepinephrine (NE) neurotransmission by DA and NA reuptake inhibition (Schmeichel and Berridge, 2013), while MDMA mainly releases serotonin (5-hydroxytryptamine, 5-HT) but also NE (Hysek et al., 2012b). While DA is thought to facilitate sexual drive, 5-HT is stated to inhibit sexual arousal and function (Fabre-Nys, 1998; Frohmader et al., 2010; Melis and Argiolas, 1995; Passie et al., 2005; Pfaus, 2009; Zemishlany et al., 2001). For example, dopaminergic antiparkinson therapy is associated with hypersexuality (Kelley et al., 2012; Uitti et al., 1989; Weintraub et al., 2010) whereas decreased libido and sexual dysfunction are common adverse effects of serotonergic antidepressants (Serretti and Chiesa, 2009). Accordingly, we hypothesized that methylphenidate (40 mg), predominantly enhancing DA, would increase sexual arousal in a Sexual Arousal Task (SAT), while MDMA (75 mg), mainly increasing 5-HT, would not. Because sex hormones may alter sexual arousal (Meston and Frohlich, 2000), we measured testosterone, estrogen, and progesterone plasma levels and explored possible associations with sexual arousal ratings.

Besides from having effects on sexual desire and emotion, psychoactive drugs may also influence aspects of the cognitive appraisal of romantic partnerships. For example, MDMA has been shown to acutely alter related components of social cognition including recognition of facial emotions (Bedi et al., 2010; Hysek et al., 2012a; Hysek et al., 2013; Hysek et al., 2014; Kirkpatrick et al., 2014) and emotional empathy (Hysek et al., 2013; Kuypers et al., 2014; Schmid et al., 2014). Additionally, changes in 5-HT levels may influence cognitions sustaining intimate relationships. Specifically, healthy volunteers perceived photographed couples as being less intimate and romantic after lowering cerebral 5-HT levels by tryptophan depletion (Bilderbeck et al., 2011). In contrast, sub-chronic administration of the selective 5-HT reuptake inhibitor (SSRI) citalopram increased perceived

worth of mutual trust in relationships and reduced importance attributed to physical and intimate aspects of the participants' own relationship (Bilderbeck et al., 2014). We therefore evaluated the effect of a 5-HT releaser (MDMA) and a DA and NA reuptake inhibitor (methylphenidate) on cognitive appraisal of intimate relationships. We hypothesized that MDMA, but not methylphenidate, would increase ratings of intimacy and romance in the Couples Appraisal Task (CAT) (Bilderbeck et al., 2011; Bilderbeck et al., 2014) parallel to its 5-HT enhancing, empathogenic and prosocial effects (Hysek et al., 2013; Kirkpatrick et al., 2014).

Experimental Procedures

Experimental protocol

We used a double-blind, placebo-controlled, cross-over design in 30 subjects each treated with methylphenidate (40mg), MDMA (75 mg), and placebo, resulting in 90 assessments. The order of the three experimental sessions was balanced (Latin Square design), and the washout periods between sessions were at least seven days. The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee and the Swiss Agency for Therapeutic Products (Swissmedic). The study was registered at ClinicalTrials.gov (NCT01616407). All of the subjects provided written informed consent before participating in the study and were paid for their participation.

Participants

Thirty healthy subjects (15 men, 15 women) with a mean age of 24 ± 4.2 years (mean ± SD; range 18 to 32 years) were recruited from the University of Basel. All subjects were self-reported heterosexuals. Inclusion criteria were age 18 to 45 years and body mass index 18 to 27 kg/m^2. The exclusion criteria were a history of psychiatric disorders (determined by the

Structured Clinical Interview for Axis I and II Disorders according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition) or chronic or acute physical illness (assessed by physical examination, electrocardiogram, standard hematology, and chemical blood analysis). Additional exclusion criteria were pregnancy, tobacco smoking (>10 cigarettes/day), a lifetime history of using illicit drugs more than five times, with the exception of past cannabis use, and any illicit drug use including cannabis within the last two months or during the study period, determined by urine tests conducted during screening and before the test sessions using TRIAGE 8 (Biosite, San Diego, California). Twenty-two subjects were "ecstasy"/MDMA-naive. Eight subjects had used MDMA less than five times. One subject reported previous single use of methylphenidate as cognitive enhancer. Six female participants used hormonal contraception. The female subjects who did not use hormonal contraception were investigated during the follicular phase (day 2 to 14).

Study drugs

±MDMA hydrochloride (Lipomed AG, Arlesheim, Switzerland) was prepared as gelatin capsules with mannitol as filler. Identical placebo (only mannitol) capsules were prepared. MDMA was administered in a single absolute dose of 75 mg corresponding to 1.1 ± 0.13 mg/kg body weight (range 0.8-1.3 mg/kg body weight). This dose of MDMA corresponds to that typically found in a single ecstasy pill (Brunt et al., 2012). Immediate-release methylphenidate tablets (4×10 mg, Ritalin, Novartis AG, Bern, Switzerland) were encapsulated within opaque gelatin capsules (with mannitol as filler), and identical placebo capsules (mannitol pill plus mannitol filler) were prepared. This is a typical and well-tolerated clinical and research dose of methylphenidate (Korostenskaja et al., 2008) producing similar cardiovascular stimulation to the dose of MDMA used (Schmid et al., 2014).

Study procedures

The experimental sessions took place in a quiet hospital research ward with no more than two research subjects of the same sex present per session. Before the first session, subjects completed a brief training to get familiarized with the computer tasks. Drug administration was at 10:00 AM. The SAT and CAT were performed at 150 and 170 minutes after drug administration, respectively, when maximal plasma levels of the drugs were expected (Hysek et al., 2014). The actual times to peak concentration were (mean±SD) 153±50 and 130±48 min after MDMA and methylphenidate administration, respectively, as reported together with the concentration-time curves (Schmid et al., 2014). A standardised small lunch was served at 13:30 PM. Subjects were sent home at 4:30 PM. During the day, subjective effects, vital signs and adverse drug effects were assessed as reported elsewhere (Schmid et al., 2014). Additional test of emotion recognition and empathy were performed 75-105 min after drug administration as reported elsewhere (Schmid et al., 2014).

Measures

Sexual Arousal Task

The SAT included 16 colour photographs taken 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 persons without sexual signals. Erotic pictures included four implicit sexual scenes (i.e., no primary or secondary sexual organs are shown explicitly but persons where shown in stimulating poses showing some skin) and four explicit sexual scenes (i.e., clearly pornographic poses or scenes). In the neutral (persons), implicit and explicit condition, two pictures with single persons and two pictures with couples were shown, respectively. Thus, we had four pictures of neutral objects (two) and landscapes (two), four pictures of neutral persons (two singles and two couples), four pictures of implicit sexual scenes (two singles and two couples), and four pictures of explicit erotic scenes (two singles and two couples). Additionally, there was a male and a female version of the test: female subjects were only shown males in the single person condition, while male subjects received

only female single person stimuli. Because men and women were tested on different tasks, scores cannot be compared directly. The SAT included two subtasks, an “effort task” and an “arousal rating task”. In the effort task, pictures were shown for one sec. To prolong the presentation, participants were instructed to click rapidly on the keyboard for as long as they wanted to see the picture. One or more clicks per sec resulted in a prolongation of the presentation by another sec until no more clicks occurred within one sec. Outcome measures were the total number of clicks and the resulting duration the picture was presented. In the arousal rating task, participants were asked to rate each picture on 5 dimensions. The dimensions included “pleasant”, “arousing/exciting”, “attractive”, “likeable”, and “erotic”. The original Self-Assessment Manikin were 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 performed on a 9-point rating scale marked “not at all” on the left and “very” on the right end. Ratings of all neutral, implicit sexual or explicit sexual pictures were averaged for each dimension. The SAT was implemented in Presentation Version 14.8 (Neurobehavioral Systems, Albany, CA, USA) and shown on a computer screen.

Couples Appraisal Task

To assess the appraisal of intimate relationships we used a German adaptation of the previously described CAT (Bilderbeck et al., 2011; Bilderbeck et al., 2014). Briefly, 18 photographs of heterosexual couples in genuine relationships were presented on a computer screen. All facial expressions were broadly neutral. Nine couples showed physical contact such as affiliative or romantic gestures and nine couples were standing apart and were not touching each other. Touching and non-touching couples were randomly mixed. Participants rated each couple using visual analogue scales (0-10) with “not at all” and “very” as anchor points for the following descriptors, which were selected to display subjects’ perceived ratings of relationship stability (Bilderbeck et al., 2011; Bilderbeck et al., 2014): “intimate”, “romantic”, “supportive”, “trusting”, “conflict resolution”, “enduring”, and “good physical

relationship". Ratings of "turbulence" and "bickering" were used as negative relationship characteristics. Additionally, "dominance" and "balance of love" were rated using scales labelled with "man" on the left and "woman" on the right, with "neutral" at the midpoint. Participants' ratings for each of the descriptors were then averaged over touching and non-touching couples. The CAT was also implemented in Presentation Version 14.8 (Neurobehavioral Systems, Albany, CA, USA).

Endocrine measures

Plasma levels of testosterone (men and women), estradiol and progesterone (only women) were measured at baseline and 2 h after drug administration using commercial electro-chemiluminescence immunoassays (Cobas ®, Roche Diagnostics, Basel, Switzerland).

Data analysis

Statistical analysis was performed using Statistica 12 (StatSoft, Tulsa, OK, USA). SAT data were analysed using analyses of variance (ANOVAs) with drug (methylphenidate, MDMA, placebo) and sexual content (neutral, implicit, explicit) as within-subject factors. Drug effects on ratings of couples in the CAT were similarly analysed using ANOVAs with drug and touching (touching vs. non-touching) as within-subject factor. ANOVAs were also used to compare hormone levels (differences from baseline, ΔE_{max}). Tukey post hoc were performed based on significant main effects or interactions. Sex-differences were assessed with sex added to the ANOVAs as between-subject factor for each descriptor. Additional ANOVAs were performed with drug order to exclude carry-over effects. Spearman's rank correlations were used to determine associations between measures. Differences associated with p-values lower than 0.05 (two-tailed) were considered statistically significant.

Results

Sexual Arousal Task

Data from two women and two men were missing for the SAT effort task and for two women for the SAT arousal task due to technical problems. Effects of methylphenidate and MDMA on SAT scores are shown in Table 1 and Figure 1.

In the effort subtask, there were significant drug × sexual content interactions for both the number of clicks and the duration of the presentation [$F(4,100)=2.6$; $p<0.05$ and $F(4,100)=3.0$, $p<0.05$; respectively]. There was a significant main effect of sexual content (neutral, implicit, explicit) on both the number of clicks [$F(2,50)=18.3$; $p<0.001$] and on the duration of the presentation [$F(2,50)=22.2$; $p<0.001$]. The total number of clicks was lower for explicit compared with implicit and neutral stimuli (both $p<0.001$). Both, methylphenidate and MDMA increased the number of clicks for implicit sexual stimuli compared with placebo ($p<0.001$ and $p<0.01$, respectively). Only methylphenidate also significantly increased the presentation time for the sexual implicit stimuli compared with placebo ($p<0.05$).

In the arousal subtask, there were significant main effects of sexual content (neutral, implicit, explicit) for all ratings [all $F(2,54)>50$; $p<0.001$]. Implicit sexual content increased ratings on all dimensions compared with neutral contents (all $p<0.001$, Table 1) and ratings were also mostly higher compared with explicit sexual contents (most $p<0.001$). Explicit sexual content also increased ratings of arousal/excitement, attractiveness, and erotic. There was a significant drug × sexual content interaction on ratings of “arousing/exciting” [$F(4,108) = 3.59$; $p<0.01$]. Methylphenidate significantly increased ratings of arousal/excitement compared with placebo ($p<0.01$) or MDMA ($p<0.001$) for pictures with an explicit sexual content. Methylphenidate similarly tended to increase ratings of erotic compared with placebo and MDMA [$F(4,108) = 2.17$; $p=0.08$; both post hoc tests: $p<0.05$] (Table 1). MDMA did not alter any ratings compared with placebo. The findings remained largely the same when an analysis was altered to include, for the neutral condition, only the pictures displaying persons (i.e. excluding landscape and object pictures). Finally, introducing the additional factor “number of shown persons” (singles vs. couples) did also not change the results and the

factor itself was also not significant. Surprisingly, there were no significant differences between male or female participants in any of the ratings or drug effects.

Couples Appraisal Task

Drug effects in the CAT are shown in Figure 2. There were no drug effects on any of the descriptors in the CAT, indicating that neither methylphenidate nor MDMA altered appraisal of intimate relationship. In line with previous studies (Bilderbeck et al., 2011; Bilderbeck et al., 2014), ratings of all relationship stability descriptors ("intimate", "romantic", "supportive", "trusting", "conflict resolution", "enduring", and "good physical relationship") were significantly increased for touching couples compared with couples who were standing apart [$F(1.28)>10$; $p<0.01$ for all descriptors]. Again, no sex differences or sex × drug interactions were observed.

Endocrine measures

Drug effects on plasma levels of testosterone, estradiol, and progesterone are shown in Table 2. There were no significant correlations between plasma sex hormone levels and sexual arousal ratings after any of the drugs (drug-induced changes or change scores [$\Delta_{placebo\text{-}drug}$]). There was a significant main effect of drug on testosterone in women [$F(2,28)=5.392$; $p<0.02$] with slightly higher levels after methylphenidate compared with placebo ($p<0.05$). Additionally, there was a significant main effect of drug on estradiol [$F(2,28)=4.672$; $p<0.02$], with higher levels after methylphenidate compared with MDMA ($p<0.05$).

Discussion

The present experimental study showed that healthy adults rated pictures with an explicit sexual content as more exciting after acute administration of methylphenidate compared with placebo or MDMA. Concurrently, methylphenidate increased the number of

responses (button presses) performed by the participants in order to prolong the presentation of images with an implicit sexual content and the actual presentation duration of these pictures. In contrast, MDMA had no effect on subjective arousal ratings of erotic pictures with implicit or explicit sexual content. However, similar to methylphenidate, MDMA also increased the number of responses for implicit sexual stimuli but the invested effort was too small to significantly ~~actually~~ prolong the presentation time. Surprisingly, none of the drugs altered appraisal of romantic relationships in a task previously shown to be sensitive to alterations in the 5-HT system (Bilderbeck et al., 2011; Bilderbeck et al., 2014).

Psychostimulants are believed to acutely increase sexual arousal and drive, but such effects have rarely been evaluated using actual tests and in controlled settings. Consistent with our findings, methylphenidate has previously been shown to increase self-reports of sexual desire (Volkow et al., 2007). However, the effect of methylphenidate on sexual desire was observed only after intravenous administration of methylphenidate but not after oral administration of a moderate dose of 20 mg (Volkow et al., 2007). Additionally, subjects rated their sexual desire in the absence of any sexual stimuli and while lying in a tomograph (Volkow et al., 2007). In contrast, in our study, subjects were viewing pictures with implicit and explicit sexual content and we evaluated drug effects on subjective sexual arousal elicited by these visual sexual stimuli. Moreover, we administered a higher dose of methylphenidate (40 mg), which might lead to similar plasma levels as intravenous administration of a lower dose (20 mg) in the study of Volkow and colleagues (Volkow et al., 2007). Consistent with the present findings, other stimulants with similar dopaminergic action including cocaine and methamphetamine have been subjectively reported to increase sex drive as well (Rawson et al., 2002) and are commonly linked with risk-associated sexual behaviours (Frohmader et al., 2010; Rawson et al., 2002). Furthermore, abstinent cocaine users also rated explicit erotic pictures from the IAPS as more pleasant compared with users of alcohol or heroin (Aguilar de Arcos et al., 2008).

The mechanisms underlying increased sexual arousal following administration of psychoactive substances have only partly been elucidated. It has been proposed that DA is responsible for the increase in sexual arousal following administration of methylphenidate or methamphetamine by disrupting conditioned inhibition of sexual arousal and behaviour (Volkow et al., 2007) although these drugs also enhance NE in addition to DA.

MDMA did not enhance subjective sexual arousal ratings in response to visual stimuli in the present study. However, MDMA, similar to methylphenidate, significantly increased the number of clicks to potentially prolong the presentation of the implicit but not of the explicit sexual stimuli compared with placebo. Viewing implicit erotic pictures was rated as more pleasant compared with viewing explicit pornographic pictures in all drug conditions. Thus, MDMA increased responding only for erotic stimuli that were more pleasant to view. Interviews of recreational MDMA users documented that most respondents reported feelings of emotional closeness while consuming MDMA but without the desire for penetrative sex (McElrath, 2005). However, other respondents reported that MDMA increased their sexual arousal and some (in particular gay and bisexual females) had used MDMA specifically for sexual enhancement (McElrath, 2005). Another interview study found that ecstasy use seemed to increase sexual desire but not the ability to achieve an erection or orgasm (Theall et al., 2006; Zemishlany et al., 2001). Thus, MDMA mainly seems to enhance pleasure in touching and physical closeness rather than actual sexual engagement and is also reported to impair sexual performance (Frohmader et al., 2010; Passie et al., 2005; Theall et al., 2006; Zemishlany et al., 2001). Neurochemically, MDMA enhances 5-HT and NE and weakly also DA transmission (Hysek et al., 2012b) but additionally, MDMA also releases oxytocin and prolactin (Hysek et al., 2012a; Hysek et al., 2013). Dopamine, NE and oxytocin enhance and 5-HT and prolactin inhibit sexual excitation (Kruger et al., 2005; Pfaus, 2009). Sexual dysfunction associated with serotonergic drugs has been shown to involve 5-HT_{1B}, 5-HT_2 and 5-HT_3 receptors (Fabre-Nys, 1998; Meston and Frohlich, 2000). In addition to releasing 5-HT and NE (Hysek et al., 2012b), MDMA also directly binds to serotonergic 5-HT_{2A}-, 5-HT_{2B}-, and 5-HT_{2C}-receptors (Simmler et al., 2013; Teitler et al., 1990). It is likely that the

serotonergic effects predominate in this neurochemical cocktail, resulting in the absence of sexually enhancing or even presence of impairing effects for MDMA at the doses typically used by humans.

Sexual stimuli and behaviour activate the mesolimbic DA reward system similarly to other rewarding/pleasant stimuli or drugs of abuse (Georgiadis and Kringelbach, 2012; Holstege et al., 2003). Our study findings are consistent with the role for DA in sexual arousal because methylphenidate increased sexual arousal and MDMA did not. In the case of MDMA, the additional release of NE may have had some small sexually enhancing effects, which were masked by concomitant 5-HT release, which is known to dampen sexual function (Pfaus, 2009). Consistent with our finding of increased sexual arousal after methylphenidate, the DA precursor levodopa enhanced the activation of the nucleus accumbens when subliminal sexual stimuli were shown, whereas the DA D_2-receptor antagonist haloperidol decreased activations (Oei et al., 2012). Accordingly, the DA and NE transporter inhibitor and antidepressant bupropion, which has less side effects on sexual arousal and libido than serotonergic antidepressants, increased activation of brain regions related to sexual functioning (Abler et al., 2011). Moreover, flibanserin, which enhances NE and DA while reducing 5-HT (Borsini et al., 2002), increased sexual desire in women with hypoactive sexual desire (Katz et al., 2013). Finally, dextroamphetamine and methylphenidate have been reported to reverse the sexually impairing effects of 5-HT transporter blockers and to even enhance sexual arousal and function in female and male patients with depression (Bartlik et al., 1995).

Although MDMA did not enhance sexual arousal in the present study, it appears to induce effects that may affect sexual interaction. In particular, MDMA increased feelings of closeness to others and sociability and alters sensual perception including touch (Hysek et al., 2013; Liechti et al., 2001; Schmid et al., 2014). Despite these emotional changes, MDMA did not alter the appraisal of romantic partnerships of others in the present study contrary to our expectation. It has previously been shown that presumably enhancing 5-HT tone with

citalopram across eight days increased ratings of trusting in the CAT and reduced the importance of physical and intimate aspects of the participant's own relationships (Bilderbeck et al., 2014). Contrarily, lowering cerebral 5-HT by tryptophan depletion has changed ratings of relationship characteristics of photographed couples, including decreased intimacy and romance (Bilderbeck et al., 2014). Alterations in 5-HT levels did not only influence relationship characteristic ratings but also ratings of dominance with women providing higher ratings of male dominance after 5-HT reduction (Bilderbeck et al., 2011), and decreased ratings of turbulence and bickering in men after citalopram (Bilderbeck et al., 2014). However, MDMA was administered acutely while citalopram was administered chronically probably resulting in adaptive changes to the 5-HT system (Stahl, 1998). Additionally, MDMA is also less selective for the 5-HT system than citalopram (see above). Moreover, although MDMA stimulates 5-HT release much more than citalopram, it did not alter ratings of general relationship stability or indices of dominance and discord in the CAT. Thus, we might have "overstimulated" our participants as – similar to DA and NE neurotransmission – an inverted U-shaped function has also been postulated for the 5-HT system (Roiser et al., 2006). Interestingly, MDMA produced subjective feelings of trust and openness towards others (Schmid et al., 2014), thus producing effects that were very similar to those perceived important in others after citalopram administration (Bilderbeck et al., 2014).

While pathologically low levels of testosterone result in decreased sexual interest and activity, variability in the normal/upper range is generally not considered to influence sexual interest or behavior in men (Meston and Frohlich, 2000). Similarly, estrogen and progesterone play only a minimal role in female sexual desire (Meston and Frohlich, 2000). We found that plasma levels of testosterone, estrogen, or progesterone were not associated with sexual arousal ratings in the present study. Consistently, different estrogen and progesterone levels exerted only minor effects on neural responses to explicit visual erotic stimulation in women (Abler et al., 2013).

The present study has several limitations. First, we used only single doses of MDMA and methylphenidate. However, the used doses of both drugs that produced similar cardiovascular stimulation (Schmid et al., 2014), indicating equipotent stimulant effects. Nevertheless, dose-response relationships are lacking as in most of such human neuropsychopharmacological experiments. As an important strength, we included two active drugs into the design allowing for comparisons of each active drug with both the placebo and another active drug condition. Second, only acute drug effects were assessed and the impact of chronic use of methylphenidate or MDMA on the present measures remains unknown. Third, sexual stimuli were presented without time limit. It has previously been shown that exposure to supraliminal sexual images showed activation in both arousal- but also control-related brain areas (Gillath and Canterberry, 2012). Men presumably show higher sexual drive (Baumeister et al., 2001), but may also exhibit stronger urge to control it when being consciously aroused, therefore resulting in similar arousal ratings than women. Future studies will have to examine drug-effects on subliminal exposure to sexual stimuli.

In summary, methylphenidate but not MDMA increased ratings of sexual excitation by visual stimuli with explicit sexual content but participants responded more to implicit stimuli after both drugs. Neither MDMA nor methylphenidate altered appraisal of romantic relationships of others. The findings are consistent with a role of DA in sexual drive. It remains to be studied whether sexual perception or even risk-associated sexual behavior is altered in subjects using methylphenidate chronically as a recreational drug, for cognitive enhancement, or as treatment for attention deficit hyperactivity disorder.

References

Abler, B., Kumpfmuller, D., Gron, G., Walter, M., Stingl, J., Seeringer, A., 2013. Neural correlates of erotic stimulation under different levels of female sexual hormones. PloS one 8, e54447.

Abler, B., Seeringer, A., Hartmann, A., Gron, G., Metzger, C., Walter, M., Stingl, J., 2011. Neural correlates of antidepressant-related sexual dysfunction: a placebo-controlled fMRI study on healthy males under subchronic paroxetine and bupropion. Neuropsychopharmacology 36, 1837-1847.

Aguilar de Arcos, F., Verdejo-Garcia, A., Lopez Jimenez, A., Montanez Pareja, M., Gomez Juarez, E., Arraez Sanchez, F., Perez Garcia, M., 2008. Changes in emotional response to visual stimuli with sexual content in drug abusers. Adicciones 20, 117-124.

Bartlik, B.D., Kaplan, P., Kaplan, H.S., 1995. Psychostimulants apparently reverse sexual dysfunction secondary to selective serotonin re-uptake inhibitors. J Sex Marital Ther 21, 264-271.

Baumeister, R.F., Catanese, K.R., Vohs, K.D., 2001. Is there a gender difference in strength of sex drive? Theoretical views, conceptual distinctions, and a review of relevant evidence. . Pers Soc Psychol Rev 5, 242-273.

Bedi, G., Hyman, D., de Wit, H., 2010. Is ecstasy an "empathogen"? Effects of ± 3,4-methylenedioxymethamphetamine on prosocial feelings and identification of emotional states in others. Biol Psychiatry 68, 1134-1140.

Bilderbeck, A.C., McCabe, C., Wakeley, J., McGlone, F., Harris, T., Cowen, P.J., Rogers, R.D., 2011. Serotonergic activity influences the cognitive appraisal of close intimate relationships in healthy adults. Biol Psychiatry 69, 720-725.

Bilderbeck, A.C., Wakeley, J., Godlewska, B.R., McGlone, F., Harris, T., Cowen, P.J., Rogers, R.D., 2014. Preliminary evidence that sub-chronic citalopram triggers the re-evaluation of value in intimate partnerships. Social cognitive and affective neuroscience 9, 1419-1425.

Borsini, F., Evans, K., Jason, K., Rohde, F., Alexander, B., Pollentier, S., 2002. Pharmacology of flibanserin. CNS Drug Rev 8, 117-142.

Bradley, M.M., Lang, P.J., 1994. Measuring emotion: the self-assessment manikin and the semantic differential. J Behav Ther Exp Psychiatry 25, 49-59.

Brunt, T.M., Koeter, M.W., Niesink, R.J., van den Brink, W., 2012. Linking the pharmacological content of ecstasy tablets to the subjective experiences of drug users. Psychopharmacology (Berl) 220, 751-762.

Buffum, J., Moser, C., 1986. MDMA and human sexual function. J Psychoactive Drugs 18, 355-359.

Fabre-Nys, C., 1998. Steroid control of monoamines in relation to sexual behaviour. Rev Reprod 3, 31-41.

Frohmader, K.S., Pitchers, K.K., Balfour, M.E., Coolen, L.M., 2010. Mixing pleasures: review of the effects of drugs on sex behavior in humans and animal models. Horm Behav 58, 149-162.

Georgiadis, J.R., Kringelbach, M.L., 2012. The human sexual response cycle: brain imaging evidence linking sex to other pleasures. Prog Neurobiol 98, 49-81.

Gillath, O., Canterberry, M., 2012. Neural correlates of exposure to subliminal and supraliminal sexual cues. Social cognitive and affective neuroscience 7, 924-936.

Holstege, G., Georgiadis, J.R., Paans, A.M., Meiners, L.C., van der Graaf, F.H., Reinders, A.A., 2003. Brain activation during human male ejaculation. J Neurosci 23, 9185-9193.

Hysek, C.M., Domes, G., Liechti, M.E., 2012a. MDMA enhances "mind reading" of positive emotions and impairs "mind reading" of negative emotions. Psychopharmacology (Berl) 222, 293-302.

Hysek, C.M., Schmid, Y., Simmler, L.D., Domes, G., Heinrichs, M., Eisenegger, C., Preller, K.H., Quednow, B.B., Liechti, M.E., 2013. MDMA enhances emotional empathy and prosocial behavior. Social cognitive and affective neuroscience. doi: 10.1093/scan/nst161.

Hysek, C.M., Simmler, L.D., Nicola, V., Vischer, N., Donzelli, M., Krähenbühl, S., Grouzmann, E., Hoener, M.C., Liechti, M.E., 2012b. Duloxetine inhibits effects of MDMA ("ecstasy") in vitro and in humans in a randomized placebo-controlled laboratory study. PloS one 7, e36476.

Hysek, C.M., Simmler, L.D., Schillinger, N., Meyer, N., Schmid, Y., Donzelli, M., Grouzmann, E., Liechti, M.E., 2014. Pharmacokinetic and pharmacodynamic effects of methylphenidate and MDMA administered alone and in combination. Int J Neuropsychopharmacol 17, 371-381.

Katz, M., DeRogatis, L.R., Ackerman, R., Hedges, P., Lesko, L., Garcia, M., Jr., Sand, M., investigators, B.t., 2013. Efficacy of flibanserin in women with hypoactive sexual desire disorder: results from the BEGONIA trial. J Sex Med 10, 1807-1815.

Kelley, B.J., Duker, A.P., Chiu, P., 2012. Dopamine agonists and pathologic behaviors. Parkinsons Dis 2012, 603631.

Kirkpatrick, M.G., Lee, R., Wardle, M.C., Jacob, S., de Wit, H., 2014. Effects of MDMA and intranasal oxytocin on social and emotional processing. Neuropsychopharmacology 39, 1654-1663.

Korostenskaja, M., Kicic, D., Kahkonen, S., 2008. The effect of methylphenidate on auditory information processing in healthy volunteers: a combined EEG/MEG study. Psychopharmacology (Berl) 197, 475-486.

Kruger, T.H., Hartmann, U., Schedlowski, M., 2005. Prolactinergic and dopaminergic mechanisms underlying sexual arousal and orgasm in humans. World J Urol 23, 130-138.

Kuypers, K.P., de la Torre, R., Farre, M., Yubero-Lahoz, S., Dziobek, I., Van den Bos, W., Ramaekers, J.G., 2014. No evidence that MDMA-induced enhancement of emotional

empathy is related to peripheral oxytocin levels or 5-HT_{1a} receptor activation. PloS one 9, e100719.

Lang, P.J., Bradley, M.M., Cuthbert, B.N., 2008. International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual. University of Florida, Gainesville, FL.

Liechti, M.E., Gamma, A., Vollenweider, F.X., 2001. Gender differences in the subjective effects of MDMA. Psychopharmacology (Berl) 154, 161-168.

Maier, L.J., Liechti, M.E., Herzig, F., Schaub, M.P., 2013. To dope or not to dope: neuroenhancement with prescription drugs and drugs of abuse among Swiss university students. PloS one 8, e77967.

McElrath, K., 2005. MDMA and sexual behavior: ecstasy users' perceptions about sexuality and sexual risk. Subst Use Misuse 40, 1461-1477.

Melis, M.R., Argiolas, A., 1995. Dopamine and sexual behavior. Neurosci Biobehav Rev 19, 19-38.

Meston, C.M., Frohlich, P.F., 2000. The neurobiology of sexual function. Arch Gen Psychiatry 57, 1012-1030.

Morgan, C.J., Noronha, L.A., Muetzelfeldt, M., Fielding, A., Curran, H.V., 2013. Harms and benefits associated with psychoactive drugs: findings of an international survey of active drug users. J Psychopharmacol 27, 497-506.

Oei, N.Y., Rombouts, S.A., Soeter, R.P., van Gerven, J.M., Both, S., 2012. Dopamine modulates reward system activity during subconscious processing of sexual stimuli. Neuropsychopharmacology 37, 1729-1737.

Passie, T., Hartmann, U., Schneider, U., Emrich, H.M., Kruger, T.H., 2005. Ecstasy (MDMA) mimics the post-orgasmic state: impairment of sexual drive and function during acute

MDMA-effects may be due to increased prolactin secretion. Med Hypotheses 64, 899-903.

Pfaus, J.G., 2009. Pathways of sexual desire. J Sex Med 6, 1506-1533.

Rawson, R.A., Washton, A., Domier, C.P., Reiber, C., 2002. Drugs and sexual effects: role of drug type and gender. J Subst Abuse Treat 22, 103-108.

Roiser, J.P., Blackwell, A.D., Cools, R., Clark, L., Rubinsztein, D.C., Robbins, T.W., Sahakian, B.J., 2006. Serotonin transporter polymorphism mediates vulnerability to loss of incentive motivation following acute tryptophan depletion. Neuropsychopharmacology 31, 2264-2272.

Schmeichel, B.E., Berridge, C.W., 2013. Neurocircuitry underlying the preferential sensitivity of prefrontal catecholamines to low-dose psychostimulants. Neuropsychopharmacology 38, 1079-1084.

Schmid, Y., Hysek, C.M., Simmler, L.D., Crockett, M.J., Quednow, B.B., Liechti, M.E., 2014. Differential effects of MDMA and methylphenidate on social cognition. J Psychopharmacol 28, 847-856.

Semple, S.J., Patterson, T.L., Grant, I., 2002. Motivations associated with methamphetamine use among HIV+ men who have sex with men. J Subst Abuse Treat 22, 149-156.

Serretti, A., Chiesa, A., 2009. Treatment-emergent sexual dysfunction related to antidepressants: a meta-analysis. J Clin Psychopharmacol 29, 259-266.

Simmler, L., Buser, T., Donzelli, M., Schramm, Y., Dieu, L.H., Huwyler, J., Chaboz, S., Hoener, M., Liechti, M.E., 2013. Pharmacological characterization of designer cathinones in vitro. Br J Pharmacol 168, 458-470.

Stahl, S.M., 1998. Mechanism of action of serotonin selective reuptake inhibitors. Serotonin receptors and pathways mediate therapeutic effects and side effects. J Affect Disord 51, 215-235.

Teitler, M., Leonhardt, S., Appel, N.M., De Souza, E.B., Glennon, R.A., 1990. Receptor pharmacology of MDMA and related hallucinogens. Ann N Y Acad Sci 600, 626-638; discussion 638-629.

Theall, K.P., Elifson, K.W., Sterk, C.E., 2006. Sex, touch, and HIV risk among ecstasy users. AIDS Behav 10, 169-178.

Uitti, R.J., Tanner, C.M., Rajput, A.H., Goetz, C.G., Klawans, H.L., Thiessen, B., 1989. Hypersexuality with antiparkinsonian therapy. Clin Neuropharmacol 12, 375-383.

Volkow, N.D., Wang, G.J., Fowler, J.S., Telang, F., Jayne, M., Wong, C., 2007. Stimulant-induced enhanced sexual desire as a potential contributing factor in HIV transmission. Am J Psychiatry 164, 157-160.

Weintraub, D., Koester, J., Potenza, M.N., Siderowf, A.D., Stacy, M., Voon, V., Whetteckey, J., Wunderlich, G.R., Lang, A.E., 2010. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol 67, 589-595.

Zemishlany, Z., Aizenberg, D., Weizman, A., 2001. Subjective effects of MDMA ('Ecstasy') on human sexual function. Eur Psychiatry 16, 127-130.

Figure 1. In the Sexual Arousal Task, pictures with sexual implicit or explicit content were rated significantly more “arousing/exciting” than neutral pictures (both $p<0.001$). Methylphenidate significantly increased ratings of “arousing/exciting” for pictures with an explicit sexual content compared with placebo ($p<0.01$) or MDMA ($p<0.001$). Data are expressed as mean ± SEM in 28 participants. **$p < 0.01$ and ***$p < 0.001$ for significant differences. Pla, placebo; MPH, methylphenidate; MDMA, 3,4-methylenedioxymethamphetamine.

Figure 2. In the Couples Appraisal Task, neither methylphenidate nor MDMA altered appraisal of intimate relationships compared with placebo. Data are expressed as mean ± SEM in 30 participants. MDMA, 3,4-methylenedioxymethamphetamine.

Table 1

Table 1. Drug effects in the Sexual Arousal Task.

	Placebo			Methylphenidate			MDMA	
	neutral	implicit sexual	explicit sexual	neutral	implicit sexual	explicit sexual	neutral	implicit sexual
Effort Task								
number of clicks	4.96±0.72	3.50±0.70	2.35±0.60^{+++}	6.27±0.80	5.81±0.74***	2.85±0.74^{+++}	5.31±0.90	5.58±0.79**
duration of presentation (sec)	3.12±0.38	2.38±0.41	1.35±0.35^{+++}	3.23±0.39	3.42±0.40*	1.46±0.38^{+++}	2.81±0.43	3.23±0.39
Arousal Rating Task								
pleasant	5.70±0.18	6.38±0.23^{+++}	4.59±0.23^{+++}	5.81±0.13	6.78±0.15^{+++}	5.05±0.25^{++}	5.76±0.15	6.72±0.20^{++}
arousing/exciting	3.66±0.18	5.81±0.24^{+++}	5.33±0.30^{+++}	3.79±0.16	6.13±0.15^{+++}	6.06±0.22$^{**\#\#\#+++}$	3.83±0.19	5.95±0.21^{+++}
attractive	4.10±0.21	6.56±0.27^{+++}	4.75±0.27^{++}	4.35±0.17	6.84±0.16^{+++}	5.22±0.25^{+++}	4.25±0.18	6.74±0.20^{+++}
likeable	4.64±0.23	6.15±0.23^{+++}	4.07±0.23^{+}	5.00±0.19	6.34±0.17^{+++}	4.35±0.20^{++}	4.75±0.23	6.38±0.21^{+++}
erotic	2.94±0.17	5.84±0.31^{+++}	5.25±0.36^{+++}	3.09±0.15	6.31±0.23^{+++}	5.84±0.30^{+++}	3.15±0.19	5.96±0.23^{+++}

Values are mean±SEM in 26 subjects (effort task) and 28 subjects (arousal task). *p < 0.05, ** p < 0.01 and ***p < 0.001 compared with placebo; $^{\#\#\#}$ p < 0.001 compared with MDMA (same s < 0.05, $^{++}$ p < 0.01, $^{+++}$ p < 0.001 compared with the respective neutral stimuli (same drug condition).

Table 2

Table 2. Endocrine measures.

		Placebo	Methylphenidate	MDMA
Testosterone (nmol/l)				
men	baseline	19.8±1.54	20.3±1.37	20.9±1.59
	at 120 min	18.9±1.50	19.5±1.41	19.8±1.65
	ΔE_{max}	-0.89±0.86	-0.81±0.85	-1.62±0.74
women	baseline	1.01±0.10	1.01±0.11	1.10±0.11
	at 120 min	0.79±0.10	0.99±0.12	0.99±0.12
	ΔE_{max}	-0.22±0.04	-0.03±0.05*	-0.10±0.05
Progesterone (nmol/l)				
women	baseline	2.90±0.82	2.28±0.31	6.93±4.32
	at 120 min	2.37±0.75	1.91±0.27	5.91±3.28
	ΔE_{max}	-0.53±0.10	-0.37±0.11	-1.02±1.10
Estradiol (pmol/l)				
women	baseline	93±16	162±63	163±39
	at 120 min	90±14	176.67±61	154±37
	ΔE_{max}	-2.85±5.19	14.5±6.24#	-8.6±7.22

Values are mean ± SEM in 15 subjects. * $p < 0.05$ compared with placebo. # $p < 0.05$ compared with MDMA.

Figure 1

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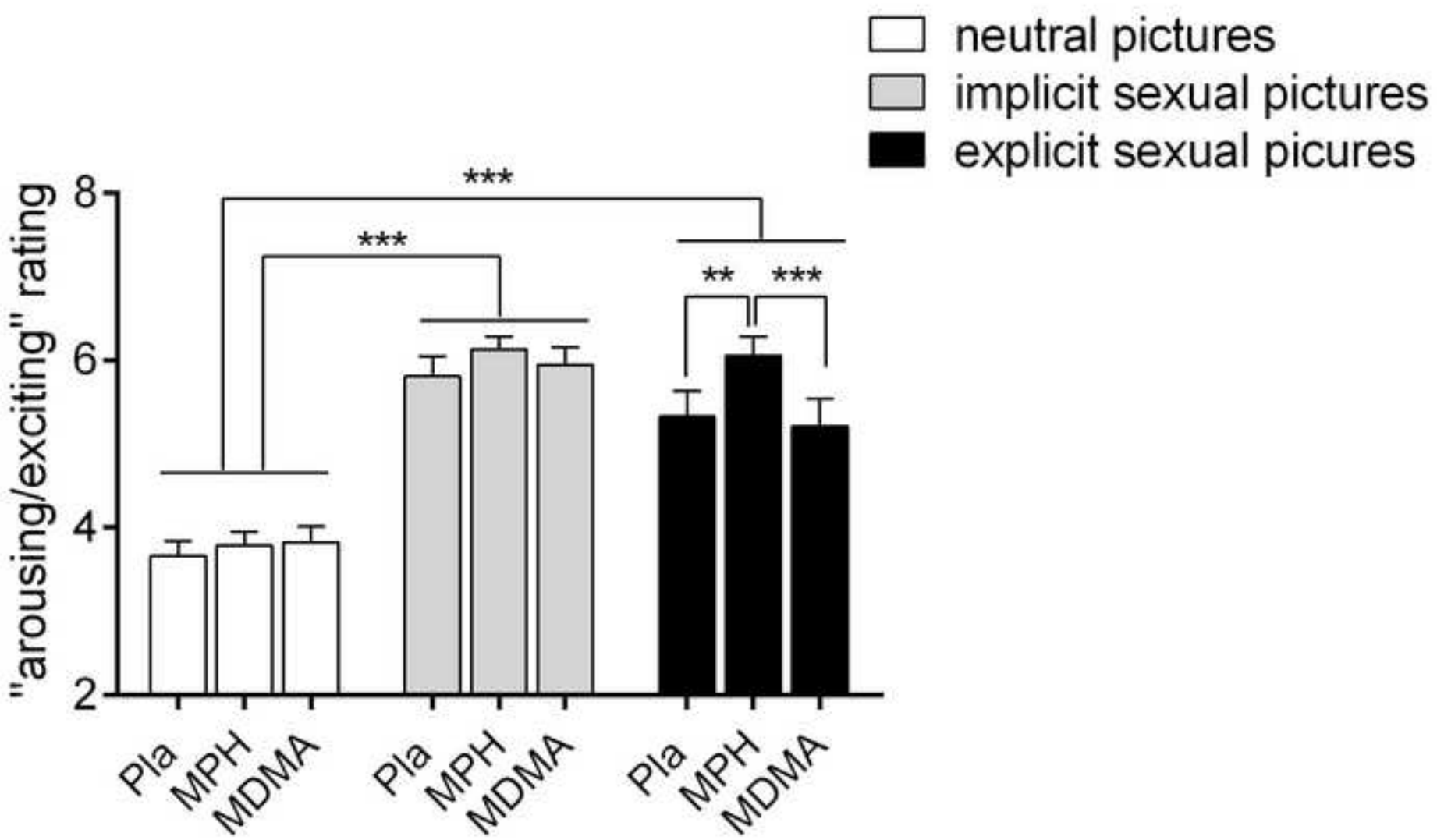

Figure 2
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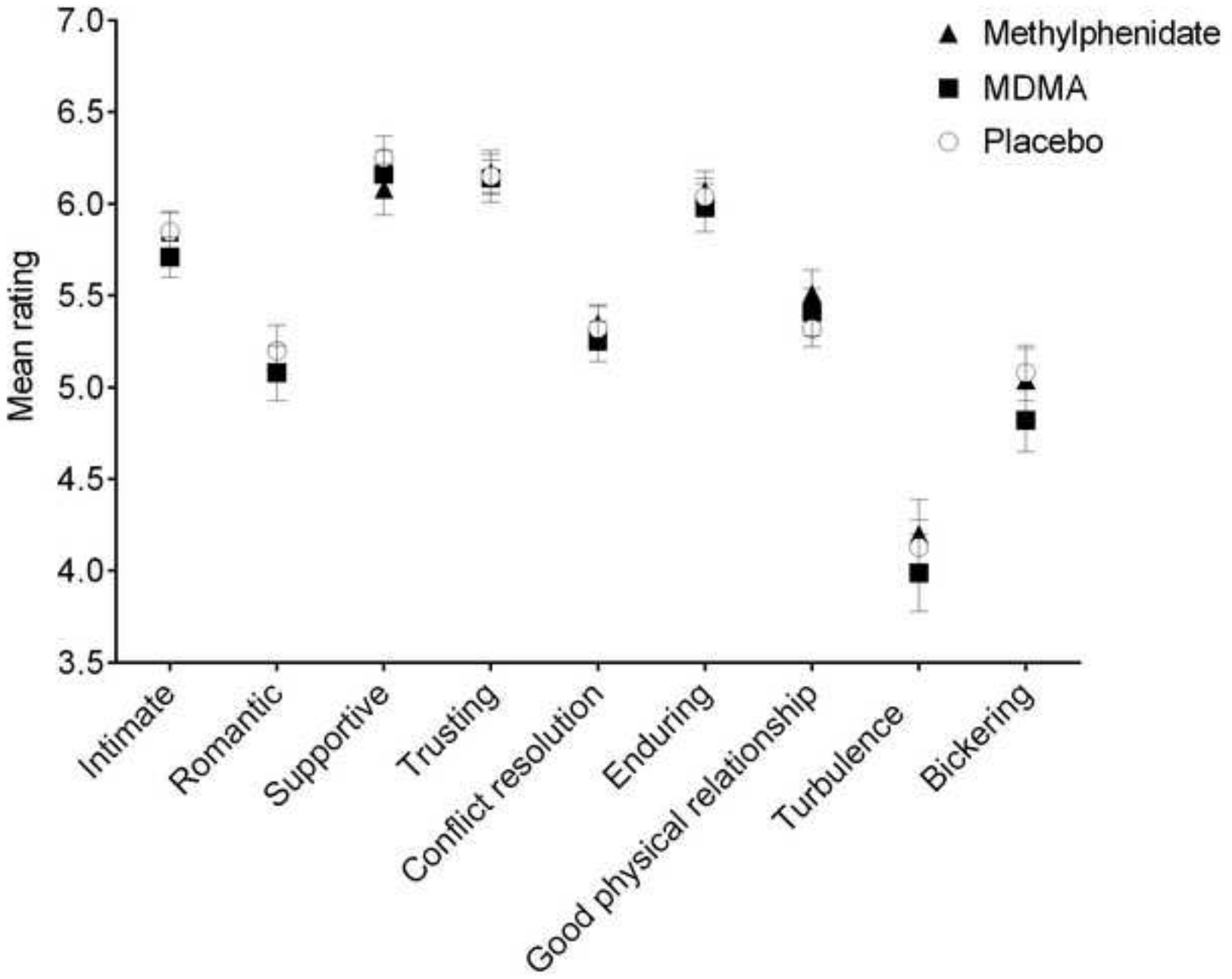

Role of funding source

This work was supported by the Swiss National Science Foundation (grant no. 32323B_144996 and 320030_149493 to MEL) and the University of Basel (grant no. DPH 2053 to CMH and DPH 2064 to MEL).

Contributors

YS, CMH, BBQ, and MEL designed the study. MEL obtained funding. MEL wrote the study protocol. YS and CMH conducted the study. YS, CMH and MEL analyzed the data. KHP, OGB, ACB, RDR, and BBQ designed and contributed tests. YS and MEL wrote the manuscript. All of the authors reviewed and approved the manuscript.

Conflict of interest

All authors declare no conflicts of interest.

Acknowledgement

The authors acknowledge the assistance of T. Schmid and L. C. Phuong in study management and A. Baumberger for instructions on the SAT and test analysis.