Published in final edited form as:

Psychophysiology. 2015 March ; 52(3): 429–435. doi:10.1111/psyp.12327.

Acute Effects of MDMA on Autonomic Cardiac Activity and Their Relation to Subjective Pro-social and Stimulant Effects

Christine M. Clark, MD¹, Charles G. Frye¹, Margaret C. Wardle, PhD², Greg J. Norman, PhD³, and Harriet de Wit, PhD¹

¹Department of Psychiatry and Behavioral Neurosciences, University of Chicago

²Department of Psychology and Behavioral Sciences, University of Texas Health Science Center at Houston

³Department of Psychology, University of Chicago

Abstract

MDMA is a stimulant with unique “pro-social” effects, the physiological and pharmacological mechanisms of which are unknown. Here we examine the relationship of measures of parasympathetic and sympathetic nervous system activity to the pro-social effects of MDMA. Parasympathetic activity was measured using respiratory sinus arrhythmia (RSA) and sympathetic activity using pre-ejection period (PEP). Over three sessions, 33 healthy volunteers received placebo, 0.75 mg/kg and 1.5 mg/kg MDMA under counterbalanced, double-blind conditions, while we measured subjective feelings, RSA, and PEP. RSA and PEP data were available for 26 and 21 participants, respectively. MDMA increased pro-social and stimulated feelings, decreased RSA and decreased PEP. At 1.5mg/kg, subjective pro-social effects correlated with stimulated feelings and PEP, but not RSA. This suggests sympathetic, rather than parasympathetic, effects relate to the pro-social effects of MDMA.

Introduction

3,4 methylenedioxymethamphetamine (MDMA, “ecstasy”) is a popular recreational drug that is also under investigation as an adjunct to psychotherapy for Post-Traumatic Stress Disorder (PTSD; Mithoefer, Wagner, Mithoefer, Jerome, & Doblin, 2011; Mithoefer et al., 2013). MDMA has unique pro-social or “empathogenic” effects that may underlie both its recreational and therapeutic use (Oehen, Traber, Widmer, & Schnyder, 2013; Sumnall, Cole, & Jerome, 2006; Ter Bogt & Engels, 2005), including increased feelings of love, insight, and desire to socialize (Bedi, Hyman, & de Wit, 2010; Kirkpatrick, Lee, Wardle, Jacob, & de Wit, in press). However, the physiological and pharmacological basis of these pro-social effects is unclear.

In this paper, we examine acute effects of MDMA on the autonomic nervous system using respiratory sinus arrhythmia (RSA) and pre-ejection period (PEP). RSA, a rhythmic

fluctuation of heart rate during respiration, measures parasympathetic cardiac control (Berntson et al., 1997). RSA is an index and potential mechanism of positive emotionality, social engagement, and emotional regulation (Appelhans & Luecken, 2006; Geisler, Kubiak, Siewert, & Weber, 2013; Geisler, Vennewald, Kubiak, & Weber, 2010; Oveis et al., 2009; Porges, 2003). PEP is the period between electrical stimulation of the heart and opening of the aortic valve and measures sympathetic cardiac control (Berntson, Quigley, & Lozano, 2007). The sympathetic system is often (although not always) active in opposition to the parasympathetic system (Berntson, Norman, Hawkley, & Cacioppo, 2008). Consistently, increased sympathetic cardiac control, indicated by decreased PEP, relates to depressed mood and social isolation (Cacioppo et al., 2002; Koschke et al., 2009; Light, Kothandapani, & Allen, 1998).

Unlike other stimulant drugs which acutely reduce parasympathetic and increase sympathetic activation, (Newlin, 1995; Perez-Reyes et al., 1991; Pohl, Balon, Jayaraman, Doll, & Yeragani, 2003; Vongpatanasin, Taylor, & Victor, 2004), it appears possible that MDMA could acutely increase parasympathetic activity. MDMA differs from other stimulants in its pro-social effects (Bedi et al., 2010), and while the exact mechanism of these effects is unknown, oxytocin is thought to play an important role. Antagonizing oxytocin blocks MDMA-induced increases in pro-social behavior in rats (Thompson, Callaghan, Hunt, Cornish, & McGregor, 2007). In humans, MDMA increases blood oxytocin, and these increases correlated with increased pro-social feelings (Dumont et al., 2009). Acute administration of oxytocin increases RSA and decreases PEP, indicating increased parasympathetic *and* sympathetic control (Kemp et al., 2012; Norman et al., 2010). Thus, it could be hypothesized that MDMA may also increase both parasympathetic and sympathetic activity through a mechanism involving oxytocin. This would provide a physiological explanation for the unique pro-social effects of MDMA compared to other stimulants. On the other hand, there is also reason to believe that MDMA may act as a typical stimulant, decreasing parasympathetic and increasing sympathetic activity. In addition to positive emotionality, parasympathetic activity is also associated with emotional regulation (Thayer & Lane, 2009). MDMA induces strong emotions (albeit positive ones), likely dysregulating emotional control, which may relate to a decrease in parasympathetic activity. Additionally, a previous study using pupillometry combined with pharmacological challenges suggested that MDMA decreases parasympathetic nervous system activity, and that this decrease correlates with its subjective effects (Hysek & Liechti, 2012). To test these two possibilities, we examined the acute effects of MDMA on simultaneous measures of parasympathetic and sympathetic autonomic cardiac control using RSA and PEP, and examined the relationship of these physiological measures to the subjective pro-social and stimulant effects of the drug.

Method

Design

This is a secondary analysis of a previous study (Frye, Wardle, Norman, & de Wit, 2014) investigating the effects of MDMA on subjective and RSA responses to simulated social rejection. The within-subject design consisted of three sessions during which 36 healthy

volunteers received placebo, 0.75mg/kg of MDMA, and 1.5mg/kg MDMA (up to a maximum dose of 125mg) in counterbalanced order under double-blind conditions. At 30-60min intervals over a 5hr session we obtained subjective and cardiovascular measures. At expected peak effect participants completed behavioral measures reported elsewhere (Frye et al., 2014). Sessions were separated by at least 96 hours. The current paper differs from the previous analysis in that in 33 of the 36 individuals we repeatedly measured RSA and PEP at rest, rather than RSA only. Thus, in the current paper we examine both autonomic measures and their relationship to the subjective effects of MDMA across the full drug time-course.

Participants

Thirty-three healthy volunteers (17 female, 16 male) were recruited through flyers, posters, and word of mouth. Participants completed a 2 hr screening that included a physical examination by a doctor, ECG, modified structural Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1996), and self reported health and drug use history. This screening was used to determine inclusion and exclusion criteria as described in Frye et al. (2014). Participants were primarily Caucasian (67%), in their 20s ($M = 24.5$ years, $SD = 4.72$), with some college education ($M = 15$ years, $SD = 1.5$), and light to moderate drug use, with an average 10 previous uses of MDMA ($SD = 8.6$, see Frye et al., 2014 Table 1 for other drug use).

Participants were instructed to refrain from alcohol and over-the-counter drugs 24hrs before and 12hrs after the session, from marijuana 7 days before and 24hrs after the session, and from all other recreational drugs 48hrs before and 24hrs after the session, and to maintain typical caffeine and nicotine intake and fast for 2hrs before each session. Compliance was verified using breath (Alcosensor III, Intoximeters Inc., St. Louis, MO) and urine tests (ToxCup, Branan Medical Corporation, Irvine, CA). Female participants were urine pregnancy tested before each session, and women not on hormonal birth control were scheduled only during the follicular phase (White, 2002). Participants were told that they might receive a sedative, stimulant, marijuana-like drug, or placebo. All participants provided informed consent, and all procedures were approved by the University of Chicago Institutional Review Board and carried out in accordance with the Declaration of Helsinki.

Procedure

Participants completed three 5hr individual study sessions. They arrived at 9:00 am, completed a urine and breath test, and ate a snack. Electrodes for cardiac and impedance monitoring were applied, and baseline measures of subjective drug effects, electrocardiogram (ECG) and thoracic impedance were obtained. All ECG and thoracic impedance recordings consisted of a five-minute period taken while participants were seated at rest. At 9:30 am, participants took two opaque sized 00 gelatin capsules containing 0.75 or 1.5mg/kg of body weight MDMA with dextrose filler, or dextrose only (placebo). At 10:00, measures of subjective drug effects, ECG, and thoracic impedance were recorded. At 10:30, subjective drug effects were recorded, but not ECG and thoracic impedance, due to conflict with another measure. From 10:30 through 12:15, behavioral tasks were completed (presented elsewhere; Frye et al., 2014). At 11:30, 12:30, 1:00, and 1:30pm, subjective drug

effects, ECG and thoracic impedance were recorded. After the 1:30 measures, ECG sensors were removed, and participants were allowed to leave, provided they reported no drug effects and their cardiovascular measures were within a normal range.

Measures

Subjective drug effects—Subjective drug effects were measured using a visual analog scale (VAS) previously validated with MDMA (Bedi et al., 2010), comprised of 13 adjectives such as “Playful”, “Stimulated”, and “Elated”, each rated on a 1-100 (not at all – extremely) line. To reduce the number of analyses, we focused on ‘Loving’ and ‘Insightful’ as representative “pro-social” effects (Bedi et al., 2010; Kirkpatrick et al., in press) and ‘Anxious’ and ‘Stimulated’ as representative stimulant effects.

Autonomic measures—ECG and thoracic impedance were measured using seven disposable self-adhesive electrodes on the participant’s back and chest in a standard lead II configuration for ECG and in a tetrapolar electrode configuration for impedance (Sherwood et al., 1990). Signals were processed by an integrated Mindware Bionex system (Mindware, Gahanna, OH). After visual inspection for artifacts, ECG and impedance waveforms were analyzed using Mindware Heart Rate Variability Analysis Software v2.51 and Impedance Software v2.6.

From these traces we derived four measures: 1. Heart rate (HR) in beats per minute (BPM). 2. Respiratory sinus arrhythmia (RSA) in the natural log of the heart period variance in the respiratory band (0.12 – 0.40Hz), obtained as described in Frye, et al. (2014). 3. Pre-Ejection Period (PEP) in milliseconds (ms), obtained by ensemble averaging ECG and impedance data and estimating time between the ECG Q wave and the dZ/dt B point. 4. Respiration rate in breaths per minute, derived from thoracic impedance (Ernst, Litvack, Lozano, Cacioppo, & Berntson, 1999), to ensure that MDMA did not significantly alter breathing pace, which could affect RSA (Berntson et al., 2007). As previously described (Berntson et al., 1997; Berntson, Norman, Hawkley, & Cacioppo, 2008), autonomic measures were obtained in 1-minute intervals during each five minute recording period and subsequently averaged to produce the value for that time point.

Statistical Analyses

Primary analyses were Drug $\times$ Time repeated-measures ANOVA, with Greenhouse-Geisser corrections for violations of sphericity, where detected. Significant Drug $\times$ Time interactions were followed up using paired-sample t-tests comparing placebo to 0.75mg/kg and 1.5mg/kg MDMA at each time point. Due to errors in data collection, 7 participants did not have complete RSA, HR, and respiration rate data, leaving $n = 26$ for these analyses, while 12 participants had incomplete PEP data, leaving $n = 21$ for these analyses. One participant was missing subjective data, leaving $n = 32$ for these analyses.

To examine relationships between subjective and autonomic effects of the drug, we subtracted baseline scores from all subsequent scores in the same session and calculated the area under the curve (AUC) of those difference scores. These AUC scores summarize total effect of each drug condition on each measure of interest (note that in the event that scores

decrease relative to baseline, the AUC will be a negative number, but this is not problematic, as the AUC continues to accurately summarize the change in that variable over the entire session). We then subtracted placebo AUC scores from 0.75mg/kg and 1.5mg/kg AUC scores, producing AUC change scores indicating the overall effect of the 0.75mg/kg and 1.5mg/kg doses on each outcome controlling for placebo effects on that same outcome (note that in the event that MDMA produces an overall decrease in a variable compared to placebo, this will be a negative number, but again, this is not problematic as this still accurately summarizes the overall effect of MDMA on that variable *compared to placebo*). We then conducted two sets of correlations, correlating across the 0.75mg/kg AUC change scores to examine relationship between drug effects at 0.75mg/kg, and correlating across the 1.5mg/kg AUC change scores to examine relationships between drug effects at 1.5mg/kg. A significant correlation would then indicate that the overall effect of the drug on a particular outcome (controlling for placebo) is related to the overall effect of the drug on another outcome (controlling for placebo). We did not use corrected p-values for these exploratory correlations, but correlations significant at $p < 0.002$ would meet a Bonferroni-corrected standard.

Results

Subjective Drug Effects

MDMA increased pro-social feelings of 'Loving' and 'Insightful'; Loving Drug $\times$ Time interaction (Greenhouse-Geisser corrected): $F(6, 200) = 2.64, p = 0.02, n^2_p = 0.08$, Fig. 1a; Insightful Drug $\times$ Time interaction (Greenhouse-Geisser corrected): $F(7, 207) = 2.59, p = 0.02, n^2_p = 0.08$, Fig. 1b. Follow up t-tests comparing drug to placebo at each time point indicated that both doses increased pro-social feelings relative to placebo, primarily from 120-180min post-capsule. When examined relative to respective session baselines, placebo slightly decreased feelings of 'Loving' at 120min, but produced no changes in 'Insightful'. MDMA (1.5mg/kg and 0.75mg/kg) increased both 'Loving' and 'Insightful' compared to baseline, primarily from 180-240min. MDMA also increased prototypical stimulant effects 'Anxious' and 'Stimulated'; Anxious Drug $\times$ Time interaction (Greenhouse-Geisser corrected): $F(5, 154) = 4.31, p = 0.001, n^2_p = 0.12$, Fig 1c; Stimulated Drug $\times$ Time interaction (Greenhouse-Geisser corrected): $F(6, 191) = 9.66, p < 0.001, n^2_p = 0.24$, See Fig. 1d. Follow up t-tests comparing drug to placebo at each time point indicated that both doses increased stimulant effects compared to placebo, primarily from 60-210min post-capsule. When examined relative to respective session baselines, placebo resulted in slightly decreased feelings of 'Anxious' at 120min and 240min, but produced no changes in 'Stimulated'. MDMA (1.5mg/kg and 0.75mg/kg) increased both typical stimulant effects compared to baseline, primarily from 60-120min.

Autonomic Measures

MDMA decreased RSA power, shortened PEP, and increased heart rate compared to placebo; RSA Drug $\times$ Time interaction: $F(10, 250) = 6.93, p < .001, n^2_p = 0.22$, Fig. 2a; PEP Drug $\times$ Time interaction (Greenhouse-Geisser corrected): $F(5, 106) = 23.65, p < .001, n^2_p = 0.54$, Fig. 2b; HR Drug $\times$ Time interaction (Greenhouse-Geisser corrected): $F(4, 105) = 22.882, p < .001, n^2_p = 0.48$, Fig 2c. Follow up t-tests comparing drug to placebo at each

time point indicated that both doses induced cardiovascular changes compared to placebo from 120min-240min post-capsule. When examined relative to respective session baselines, RSA increased relative to baseline under placebo conditions across the entire session. This is likely due to participants sitting quietly, relaxing, and becoming accustomed to the laboratory setting. Similar findings are common in our lab under placebo conditions. MDMA (1.5mg/kg) disrupted this increase, such that under MDMA RSA values were not significantly different from baseline from 120-240min. PEP was largely unaffected by placebo relative to baseline, while MDMA (0.75 and 1.5mg/kg) decreased PEP from 30 to 240min, relative to baseline. Last, HR decreased across the session under placebo conditions, was largely unchanged relative to baseline under 0.75mg/kg MDMA, and was increased relative to baseline by 1.5mg/kg MDMA. MDMA did not significantly affect respiration compared to placebo, and no consistent pattern of changes relative to baseline was observed in any drug condition; Respiration Rate Drug $\times$ Time interaction (Greenhouse-Geisser corrected): $F(7, 170) = 0.85$, $p = 0.55$, $\eta^2_p = 0.03$, Fig. 2d.

Correlations between Subjective Effects and Autonomic Response

Across both doses, increased HR correlated with decreased PEP and RSA (Table 1). Further, changes produced by the 1.5mg/kg dose in the pro-social feelings 'Loving' and 'Insightful' were positively correlated. Thus, our method of measuring changes due to drug reflected expected relationships between phenomena that should change in tandem. Unexpectedly, changes in 'Stimulating' and 'Insightful' were also positively correlated at 1.5mg/kg (Table 1).

There were only two significant correlations between subjective effects of MDMA and its autonomic effects, both of which were unexpected. At 0.75mg/kg, 'Loving' correlated with decreased heart rate, and at 1.5mg/kg, 'Loving' correlated with decreased PEP (Table 1).

Discussion

We examined the effects of MDMA on parasympathetic and sympathetic activity, and explored whether these physiological effects were associated with the subjective pro-social and stimulant effects of the drug. MDMA significantly decreased parasympathetic activity, measured with RSA power, and increased sympathetic activity, measured with PEP. MDMA increased pro-social and stimulant feelings, but subjective pro-social effects were not associated with RSA. Rather, at the high dose, subjective pro-social effects correlated with subjective stimulant effects and to some extent with increased sympathetic activity, although these finding must be considered tentative in the context of the large number of correlations examined.

Our data suggest that increases in parasympathetic activity do not underlie the pro-social effects of MDMA. This is somewhat consistent with a recent study that examined the autonomic effects of MDMA using pupillometry and found that MDMA produced inhibition of parasympathetic activity, as measured by the reduction in the pupillary light reflex (Hysek & Liechti, 2012). However, our results also differ from this previous study, which found that this *reduced* parasympathetic activity correlated with the subjective effects of MDMA. Here we did not find any associations between subjective effects and reduced

parasympathetic activity. This divergence may be in part due to use of two different measures, as pupillometry may capture central effects of MDMA while our measures were taken peripherally. Nevertheless, the consistent findings indicating reduced parasympathetic activity may have implications for the pharmacological mechanism of MDMA's pro-social effects. Oxytocin is thought to produce pro-social effects in part via activation of the parasympathetic "social nervous system" (Porges, 2003). Yet, MDMA increases pro-social feelings while reducing parasympathetic activity. Alternately, serotonin (5HT) and norepinephrine (NE) may contribute to the pro-social effects of MDMA. Co-administering a selective 5HT reuptake inhibitor or NE transporter inhibitor significantly dampens MDMA's cardiovascular and pro-social effects (Hysek et al., 2011; Hysek et al., 2012; Tancer & Johanson, 2007). SSRIs and SNRIs also decrease PEP and RSA over prolonged administration. (Davidson et al., 2005; Licht, de Geus, van Dyck, & Penninx, 2010; Licht, Penninx, & de Geus, 2012; although c.f. Pohl et al., 2003). Although tentative due to our small sample size and the large number of correlations examined, the observed relationship between pro-social, stimulant, and sympathetic effects at the 1.5mg/kg dose would be more consistent with a role for 5HT and NE in these pro-social effects than oxytocin.

Alternately, it is possible that under MDMA administration, RSA is not a good indicator of parasympathetic activity. In a previous study, researchers found evidence suggesting the effects of cocaine on RSA were mediated by the sympathetic, not the parasympathetic system (Vongpatanasin et al., 2004). This raises the possibility that RSA is not tightly coupled with parasympathetic activity during stimulant drug administration. At a minimum, the fact that RSA does not index the pro-social effects of MDMA indicates that RSA cannot be used as a biomarker of pro-social responses to MDMA in studies of MDMA-assisted psychotherapy or abuse potential.

The present study has several limitations. First, our small sample was not powered to detect smaller correlations between autonomic function and subjective experience. Second, all participants had prior MDMA experience, and Brody et al. (1998) found reduced baseline RSA in frequent MDMA users. However, their average participant used MDMA approximately once per week, while our participants averaged only 10 uses over a lifetime. Last, MDMA is typically taken in groups. Alcohol produces different subjective effects when consumed in a social group vs. isolation (Kirkpatrick & de Wit, 2013), and it is possible this also holds true for MDMA, such that individually conducted studies like this one may miss important effects.

Taken together, the present findings indicate that MDMA decreases parasympathetic activity and increases sympathetic activity while simultaneously producing subjective pro-social and stimulant effects in healthy volunteers. This finding raises an interesting possibility about the mechanisms active in MDMA-assisted psychotherapy for PTSD. Rather than activating the parasympathetic "social engagement" system, which might increase therapist/client alliance (one proposed mechanism for MDMA in therapy; Johansen & Krebs, 2009), instead, our results along with those of others (Hysek & Liechti, 2012) suggest MDMA primarily increases sympathetic arousal. Effective PTSD treatment requires emotional engagement and fear activation during trauma memory exposures (Foa, 2000), with patients experiencing higher distress and activation during initial sessions benefiting more from

treatment (Foa, Riggs, Massie, & Yarczower, 1995; Jaycox, Foa, & Morral, 1998). Thus, the sympathetic activation produced by MDMA could be contributing to the effectiveness of MDMA in psychotherapy for PTSD. The current results in healthy normal adults cannot establish that the observed sympathetic effects are indeed active in MDMA-assisted psychotherapy, but this possibility warrants further follow up in clinical trials of MDMA-assisted psychotherapy.

Acknowledgments

The authors would like to thank Celina Joos, Lindsey Davis, Aoibhin Curran and Sarah Ellefson for help with data collection and scoring, and the University of Chicago Investigational Pharmacy service for preparing the drug capsules. This work was supported by a grant from the National Institute on Drug Abuse (R01 DA002812) to Harriet de Wit, and Margaret Wardle was supported during the execution of this work by a National Institute on Drug Abuse Training Grant (T32 DA007255).

References

- Appelhans, Bradley M.; Luecken, Linda J. Heart rate variability as an index of regulated emotional responding. *Review of General Psychology*. 2006; 10(3):229. doi: 10.1037/1089-2680.10.3.229.
- Bedi, Gillinder; Hyman, David; de Wit, Harriet. Is ecstasy an “empathogen”? Effects of $\pm$ 3,4-methylenedioxymethamphetamine on prosocial feelings and identification of emotional states in others. *Biological Psychiatry*. 2010; 68(12):1134–1140. doi: 10.1016/j.biopsych.2010.08.003. [PubMed: 20947066]
- Berntson, Gary G.; Bigger, J. Thomas, Jr; Eckberg, Dwain L.; Grossman, Paul; Kaufmann, Peter G.; Malik, Marek; van der Molen, Maurits W. Heart rate variability: Origins, methods, and interpretive caveats. *Psychophysiology*. 1997; 34(6):623–648. doi: 10.1111/j.1469-8986.1997.tb02140.x. [PubMed: 9401419]
- Berntson, Gary G.; Norman, Greg J.; Hawkley, Louise C.; Cacioppo, John T. Cardiac autonomic balance versus cardiac regulatory capacity. *Psychophysiology*. 2008; 45(4):643–652. doi: 10.1111/j.1469-8986.2008.00652.x. [PubMed: 18282204]
- Berntson, Gary G.; Quigley, Karen S.; Lozano, Dave. Cardiovascular psychophysiology. In: Cacioppo, JT.; Tassinari, LG.; Berntson, GG., editors. *Handbook of psychophysiology*. Cambridge University Press; Cambridge, NY: 2007. p. 182-210.
- Brody, Stuart; Krause, Clemens; Veit, Ralf; Rau, Harald. Cardiovascular autonomic dysregulation in users of MDMA (“Ecstasy”). *Psychopharmacology*. 1998; 136(4):390–393. doi: 10.1007/s002130050582. [PubMed: 9600585]
- Cacioppo, John T.; Hawkley, Louise C.; Crawford, L. Elizabeth; Ernst, John M.; Burleson, Mary H.; Kowalewski, Ray B.; Berntson, Gary G. Loneliness and health: Potential mechanisms. *Psychosomatic Medicine*. 2002; 64(3):407–417. [PubMed: 12021415]
- Davidson, Jonathan; Watkins, Lana; Owens, Michael; Krulwicz, Stan; Connor, Kathryn; Carpenter, David; Nemeroff, Charles. Effects of paroxetine and venlafaxine XR on heart rate variability in depression. *Journal of Clinical Psychopharmacology*. 2005; 25(5):480–484. [PubMed: 16160626]
- Dumont GJH, Sweep FCGJ, van der Steen R, Hermesen R, Donders ART, Touw DJ, Verkes RJ. Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. *Social Neuroscience*. 2009; 4(4):359–366. doi: 10.1080/17470910802649470. [PubMed: 19562632]
- Ernst, John M.; Litvack, Daniel A.; Lozano, David L.; Cacioppo, John T.; Berntson, Gary G. Impedance pneumography: Noise as signal in impedance cardiography. *Psychophysiology*. 1999; 36(3):333–338. doi: 10.1017/S0048577299981003. [PubMed: 10352556]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB. *Structured clinical interview for DSM-IV axis I disorders*. Biometrics Research Department; New York: 1996.
- Foa, Edna B. Psychosocial treatment of posttraumatic stress disorder. *Journal of Clinical Psychiatry*. 2000; 61(Suppl 5):43–51. [PubMed: 10761678]

- Foa, Edna B.; Riggs, David S.; Massie, Elise D.; Yarczower, Matthew. The impact of fear activation and anger on the efficacy of exposure treatment for posttraumatic stress disorder. *Behavior Therapy*. 1995; 26(3):487–499. doi: 10.1016/S0005-7894(05)80096-6.
- Frye, Charles G.; Wardle, Margaret C.; Norman, Greg J.; de Wit, Harriet. MDMA decreases the effects of simulated social rejection. *Pharmacology Biochemistry and Behavior*. 2014; 117(0):1–6. doi: 10.1016/j.pbb.2013.11.030.
- Geisler, Fay C. M.; Kubiak, Thomas; Siewert, Kerstin; Weber, Hannelore. Cardiac vagal tone is associated with social engagement and self-regulation. *Biological Psychology*. 2013; 93(2):279–286. doi: 10.1016/j.biopsycho.2013.02.013. [PubMed: 23466587]
- Geisler, Fay C. M.; Vennewald, Nadja; Kubiak, Thomas; Weber, Hannelore. The impact of heart rate variability on subjective well-being is mediated by emotion regulation. *Personality and Individual Differences*. 2010; 49(7):723–728. doi: 10.1016/j.paid.2010.06.015.
- Hysek CM, Liechti ME. Effects of MDMA alone and after pretreatment with reboxetine, duloxetine, clonidine, carvedilol, and doxazosin on pupillary light reflex. *Psychopharmacology*. 2012; 224(3):363–376. doi: 10.1007/s00213-012-2761-6. [PubMed: 22700038]
- Hysek CM, Simmler LD, Ineichen M, Grouzmann E, Hoener MC, Brenneisen R, Liechti ME. The norepinephrine transporter inhibitor reboxetine reduces stimulant effects of MDMA (“Ecstasy”) in humans. *Clinical Pharmacology and Therapeutics*. 2011; 90(2):246–255. doi: <http://www.nature.com/clpt/journal/v90/n2/supinfo/clpt201178s1.html>. [PubMed: 21677639]
- Hysek CM, Simmler LD, Nicola VG, Vischer N, Donzelli M, Krahenbuhl S, Liechti ME. Duloxetine inhibits effects of MDMA (“ecstasy”) in vitro and in humans in a randomized placebo-controlled laboratory study. *PLoS ONE*. 2012; 7(5):e36476. doi: 10.1371/journal.pone.0036476. [PubMed: 22574166]
- Jaycox, Lisa H.; Foa, Edna B.; Morral, Andrew R. Influence of emotional engagement and habituation on exposure therapy for PTSD. *Journal of Consulting and Clinical Psychology*. 1998; 66(1):185–192. doi: 10.1037/0022-006X.66.1.185. [PubMed: 9489273]
- Johansen PØ, Krebs TS. How could MDMA (ecstasy) help anxiety disorders? A neurobiological rationale. *Journal of Psychopharmacology*. 2009; 23(4):389–391. doi: 10.1177/0269881109102787. [PubMed: 19273493]
- Kemp, Andrew H.; Quintana, Daniel S.; Kuhnert, Rebecca-Lee; Griffiths, Kristi; Hickie, Ian B.; Guastella, Adam J. Oxytocin increases heart rate variability in humans at rest: Implications for social approach-related motivation and capacity for social engagement. *PLoS ONE*. 2012; 7(8):e44014. doi: 10.1371/journal.pone.0044014. [PubMed: 22937145]
- Kirkpatrick, Matthew G.; de Wit, Harriet. In the company of others: Social factors alter acute alcohol effects. *Psychopharmacology*. 2013 doi: 10.1007/s00213-013-3147-0.
- Kirkpatrick, Matthew G.; Lee, Royce; Wardle, Margaret C.; Jacob, Suma; de Wit, Harriet. Effects of MDMA and intranasal oxytocin on social and emotional processing. *Neuropsychopharmacology*. in press. doi: 10.1038/npp.2014.12.
- Koschke, Mandy; Boettger, Michael K.; Schulz, Steffen; Berger, Sandy; Terhaar, Janneke; Voss, Andreas; Bär, Karl-Jürgen. Autonomy of autonomic dysfunction in major depression. *Psychosomatic Medicine*. 2009; 71(8):852–860. doi: 10.1097/PSY.0b013e3181b8bb7a. [PubMed: 19779146]
- Licht, Carmilla M. M.; de Geus, Eco J. C.; van Dyck, Richard; Penninx, Brenda W. J. H. Longitudinal evidence for unfavorable effects of antidepressants on heart rate variability. *Biological Psychiatry*. 2010; 68(9):861–868. doi: 10.1016/j.biopsych.2010.06.032. [PubMed: 20843507]
- Licht, Carmilla M. M.; Penninx, Brenda W. J. H.; de Geus, Eco J. C. Effects of antidepressants, but not psychopathology, on cardiac sympathetic control: a longitudinal study. *Neuropsychopharmacology*. 2012; 37(11):2487–2495. [PubMed: 22763618]
- Light, Kathleen C.; Kothandapani, Rupa V.; Allen, Michael T. Enhanced cardiovascular and catecholamine responses in women with depressive symptoms. *International Journal of Psychophysiology*. 1998; 28(2):157–166. doi: 10.1016/S0167-8760(97)00093-7. [PubMed: 9545653]
- Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. The safety and efficacy of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-

- resistant posttraumatic stress disorder: The first randomized controlled pilot study. *Journal of Psychopharmacology*. 2011; 25(4):439–452. doi: 10.1177/0269881110378371. [PubMed: 20643699]
- Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Martin SF, Yazar-Klosinski B, Doblin R. Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: A prospective long-term follow-up study. *Journal of Psychopharmacology*. 2013; 27(1):28–39. doi: 10.1177/0269881112456611. [PubMed: 23172889]
- Newlin DB. Effect of cocaine on vagal tone: A common factors approach. *Drug and Alcohol Dependence*. 1995; 37(3):211–216. doi: 10.1016/0376-8716(94)01086-Z. [PubMed: 7796715]
- Norman, Greg J.; Cacioppo, John T.; Morris, John S.; Malarkey, William B.; Berntson, Gary G.; DeVries, A. Courtney. Oxytocin increases autonomic cardiac control: Moderation by loneliness. *Biological Psychology*. 2010; 86(3):174–180. doi: 10.1016/j.biopsycho.2010.11.006. [PubMed: 21126557]
- Oehen, Peter; Traber, Rafael; Widmer, Verena; Schnyder, Ulrich. A randomized, controlled pilot study of MDMA ($\pm$ 3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). *Journal of Psychopharmacology*. 2013; 27(1):40–52. doi: 10.1177/0269881112464827. [PubMed: 23118021]
- Oveis, Christopher; Cohen, Adam B.; Gruber, June; Shiota, Michelle N.; Haidt, Jonathan; Keltner, Dacher. Resting respiratory sinus arrhythmia is associated with tonic positive emotionality. *Emotion*. 2009; 9(2):265–270. doi: 10.1037/a0015383. [PubMed: 19348538]
- Perez-Reyes, Mario; White, W. Reid; McDonald, Susan A.; Hill, Judith M.; Jeffcoat, A. Robert; Cook, C. Edgar. Clinical effects of methamphetamine vapor inhalation. *Life Sciences*. 1991; 49(13):953–959. doi: 10.1016/0024-3205(91)90078-P. [PubMed: 1886456]
- Pohl R, Balon R, Jayaraman A, Doll RG, Yeragani V. Effect of fluoxetine, pemoline and placebo on heart period and QT variability in normal humans. *Journal of Psychosomatic Research*. 2003; 55(3):247–251. [PubMed: 12932798]
- Porges, Stephen W. The Polyvagal Theory: Phylogenetic contributions to social behavior. *Physiology and Behavior*. 2003; 79(3):503–513. doi: 10.1016/s0031-9384(03)00156-2. [PubMed: 12954445]
- Sherwood, Andrew; Allen, Michael T.; Fahrenberg, Jochen; Kelsey, Robert M.; Lovallo, William R.; van Doornen, Lorenz J. P. Methodological Guidelines for Impedance Cardiography. *Psychophysiology*. 1990; 27(1):1–23. doi: 10.1111/j.1469-8986.1990.tb02171.x. [PubMed: 2187214]
- Sumnall, Harry R.; Cole, Jon C.; Jerome, Lisa. The varieties of ecstatic experience: an exploration of the subjective experiences of ecstasy. *Journal of Psychopharmacology*. 2006; 20(5):670–682. doi: 10.1177/0269881106060764. [PubMed: 16401654]
- Tancer, Manuel; Johanson, Chris-Ellyn. The effects of fluoxetine on the subjective and physiological effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology*. 2007; 189(4):565–573. doi: 10.1007/s00213-006-0576-z. [PubMed: 17047932]
- Ter, Bogt; Tom, FM.; Engels, Rutger C. M. E. “Partying” hard: party style, motives for and effects of MDMA use at rave parties. *Substance Use and Misuse*. 2005; 40(9-10):1479–1502. [PubMed: 16048829]
- Thayer, Julian F.; Lane, Richard D. Claude Bernard and the heart–brain connection: Further elaboration of a model of neurovisceral integration. *Neuroscience and Biobehavioral Reviews*. 2009; 33(2):81–88. doi: http://dx.doi.org/10.1016/j.neubiorev.2008.08.004. [PubMed: 18771686]
- Thompson MR, Callaghan PD, Hunt GE, Cornish JL, McGregor IS. A role for oxytocin and 5-HT1A receptors in the prosocial effects of 3, 4 methylenedioxymethamphetamine (“ecstasy”). *Neuroscience*. 2007; 146(2):509–514. [PubMed: 17383105]
- Vongpatanasin, Wanpen; Taylor, J. Andrew; Victor, Ronald G. Effects of cocaine on heart rate variability in healthy subjects. *The American Journal of Cardiology*. 2004; 93(3):385–388. doi: 10.1016/j.amjcard.2003.10.028. [PubMed: 14759401]

Figure 1.

MDMA dose-dependently increased the pro-social feelings of Loving (panel a) and Insightful (panel b), and the stimulant feelings of Anxious (panel c) and Stimulated (panel d), all represent means with standard error of the mean (SEM). * $p < 0.05$ difference between 1.5mg/kg and placebo, + $p < 0.05$ difference between 0.75mg/kg and placebo, # $p < 0.05$ difference between placebo at that time point and placebo baseline, & $p < 0.05$ difference between 0.75mg/kg at that time point and 0.75mg/kg baseline, % $p < 0.05$ difference between 1.5mg/kg at that time point and 1.5mg/kg baseline

Figure 2.

MDMA dose-dependently decreased Respiratory Sinus Arrhythmia (RSA; panel a), decreased Pre-Ejection Period (PEP; panel b), and increased Heart Rate (HR; panel c). MDMA did not significantly affect Respiration Rate (panel d), all represent means with standard error of the mean (SEM). * $p < 0.05$ difference between 1.5mg/kg and placebo, + $p < 0.05$ difference between 0.75mg/kg and placebo, # $p < 0.05$ difference between placebo at that time point and placebo baseline, & $p < 0.05$ difference between 0.75mg/kg at that time

point and 0.75mg/kg baseline, % $p < 0.05$ difference between 1.5mg/kg at that time point and 1.5mg/kg baseline

Correlations between Area Under the Curve (AUC) summary scores of drug effects at 0.75mg/kg and 1.5mg/kg MDMA (difference scores compared to placebo)

Table 1

	RSA		PEP		Loving		Insightful		Anxious		Stimulated	
	0.75 mg/kg	1.5 mg/kg	0.75 mg/kg	1.5 mg/kg	0.75 mg/kg	1.5 mg/kg	0.75 mg/kg	1.5 mg/kg	0.75 mg/kg	1.5 mg/kg	0.75 mg/kg	1.5 mg/kg
Heart Rate	-0.46* n = 26	-0.43* n = 28	-0.50* n = 19	-0.53* n = 25	-0.40* n = 26	0.15 n = 29	-0.08 n = 26	0.19 n = 29	0.10 n = 26	0.13 n = 29	0.20 n = 26	0.30 n = 29
RSA	--	--	0.37 n = 19	-0.02 n = 25	-0.11 n = 26	0.14 n = 28	0.003 n = 26	0.33 n = 28	0.15 n = 26	-0.10 n = 28	0.08 n = 26	0.13 n = 28
PEP	--	--	--	--	0.12 n = 20	-0.48* n = 27	-0.06 n = 20	-0.25 n = 27	0.26 n = 20	-0.19 n = 27	-0.14 n = 20	-0.13 n = 27
Loving	--	--	--	--	0.16 n = 32	--	0.16 n = 32	0.50* n = 33	-0.07 n = 32	-0.18 n = 33	0.16 n = 32	0.21 n = 33
Insightful	--	--	--	--	--	--	--	--	-0.02 n = 32	-0.03 n = 33	0.08 n = 32	0.60** n = 33
Anxious	--	--	--	--	--	--	--	--	--	--	0.34 n = 32	0.19 n = 33

RSA (respiratory sinus arrhythmia); PEP (pre-ejection period)

*
p < 0.05

**
p < 0.001