Published in final edited form as:

Neurotoxicol Teratol. 2016 ; 54: 22–28. doi:10.1016/j.ntt.2016.01.003.

Motor Delays in MDMA (Ecstasy) Exposed Infants Persist to 2 Years

Lynn T. Singer, Ph.D.^a, Derek G. Moore, Ph.D.^b, Meeyoung O. Min, Ph.D.^a, Julia Goodwin, Ph.D.^b, John J.D. Turner, Ph.D.^b, Sarah Fulton, M.S., CCC-SLP^a, and Andrew C. Parrott, Ph.D.^c

Lynn T. Singer: Lynn.Singer@case.edu; Derek G. Moore: D.G.Moore@uel.ac.uk; Meeyoung O. Min: Meeyoung.Min@case.edu; Julia Goodwin: J.E.Goodwin@uel.ac.uk; John J.D. Turner: J.J.D.Turner@uel.ac.uk; Sarah Fulton: Sarah.Fulton@case.edu; Andrew C. Parrott: a.c.parrott@swansea.ac.uk

^aCase Western Reserve University, 10900 Euclid Avenue, Cleveland, Ohio 44106, United States

^bThe University of East London, Docklands Campus, University Way, London E16 2RD, United Kingdom

^cSwansea University, Singleton Park, Swansea, Wales SA2 8PP, United Kingdom

Abstract

Background—Recreational use of 3,4 methylenedioxymethamphetamine (Ecstasy, MDMA) is increasing worldwide. Its use by pregnant women causes concern due to potentially harmful effects on the developing fetus. MDMA, an indirect monoaminergic agonist and reuptake inhibitor, affects the serotonin and dopamine systems. Preclinical studies of fetal exposure demonstrate effects on learning, motor behavior, and memory. In the first human studies, we found prenatal MDMA exposure related to poorer motor development in the first year of life. In the present study we assessed the effects of prenatal exposure to MDMA on the trajectory of child development through 2 years of age. We hypothesized that exposure would be associated with poorer mental and motor outcomes.

Materials and Methods—The DAISY (Drugs and Infancy Study, 2003–2008) employed a prospective longitudinal cohort design to assess recreational drug use during pregnancy and child outcomes in the United Kingdom. Examiners masked to drug exposures followed infants from birth to 4, 12, 18, and 24 months of age. MDMA, cocaine, alcohol, tobacco, cannabis, and other drugs were quantified through a standardized clinical interview. The Bayley Scales (III) of Mental (MDI) and Motor (PDI) Development and the Behavior Rating Scales (BRS) were primary outcome measures. Statistical analyses included a repeated measures mixed model approach controlling for multiple confounders.

Corresponding Author: Lynn T. Singer, Ph.D., Case Western Reserve University, Adelbert Hall, Room 216, 2040 Adelbert Road, Cleveland, Ohio 44106, Telephone: 01 (216) 368-4389, FAX: 01 (216) 368-4325, Lynn.Singer@case.edu.

Conflict of Interest:

There are no applicable conflicts of interests, financial or otherwise, related to the submitted manuscript and no compensation was received by anyone who contributed to this paper. All persons named have provided written permission to be named.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Results—Participants were pregnant women volunteers, primarily white, of middle class socioeconomic status, average IQ, with some college education, in stable partner relationships. Of 96 women enrolled, children of 93 had at least one follow-up assessment and 81 (87%) had two assessments. Heavier MDMA exposure, ($M = 1.3 \pm 1.4$ tablets per week) predicted lower PDI ($p < .002$), and poorer BRS motor quality from 4 to 24 months of age, but did not affect MDI, orientation, or emotional regulation. Children with heavier exposure were twice as likely to demonstrate poorer motor quality as lighter and non-exposed children ($O.R. = 2.2$, 95%, $CI = 1.02-4.70$, $p < .05$).

Discussion—Infants whose mothers reported heavier MDMA use during pregnancy had motor delays from 4 months to two years of age that were not attributable to other drug or lifestyle factors. Women of child bearing age should be cautioned about the use of MDMA and MDMA-exposed infants should be screened for motor delays and possible intervention.

Keywords

Behavior; Cocaine; Alcohol; Teratology; 3,4-Methylenedioxymethamphetamine; Infant development; Prenatal; Motor; “Ecstasy”

1. Introduction

Despite its illegal status, 3,4 methylenedioxymethamphetamine (MDMA, “Ecstasy”) has become a popular recreational drug worldwide over the past two decades, extensively used by subgroups of young adults at “rave” dance parties in the U.S., Australia, the United Kingdom, and throughout Europe (Parrott AC, 2004). While primarily taken in pill form, MDMA can also be taken as a crystalline powder in drinks, popularized by rock stars as “Molly” in the U.S. and “Mandy” in the U.K. MDMA has also been promoted as a psychotherapeutic agent for the treatment of relationship problems and PTSD (Chabrol H, 2013; Greer G & Tolbert R, 1986; Sessa B, 2011). In 2012, the United Nations Office on Drugs and Crime estimated that between 9.4 and 28.2 million people globally used MDMA at least once (Mohan J ed, June, 2014). In the U.S. it is estimated that about 6.2% of individuals 12 years of age or older had used Ecstasy.(SAMHSA Center for Behavioral Health Statistics and Quality, 2013)

MDMA is a ring substituted methamphetamine derivative and a powerful, indirect monoaminergic agonist that inhibits the reuptake and promotes the release of serotonin and dopamine. It also affects noradrenaline, acetylcholine, and histamine (Green AR, Mechan AO, Elliott JM, O'Shea E, & Colado MI, 2003), produces oxytocin release (Kirkpatrick MG, Lee R, Wardle MC, Jacob S, & de Wit H, 2014) and reverses the action of the serotonin transporter (SERT) leading to depletion of up to 80% of available serotonin with use (Ricaurte GA, Yuan J, & McCann UD, 2000).

Adult use of this central nervous system stimulant with hallucinogenic properties is associated with multiple acute and chronic physiological, emotional and cognitive effects. Immediate feelings of energy, sociability, euphoria, enhanced sensory perception, and emotional connectedness frequently give way to depressive symptoms and executive function and memory impairments with chronic use (Parrott AC, 2013). Current data

suggest MDMA is more likely to be used by women (Wu LT, Parrott AC, Ringwalt CL, Yang C, & Blazer DG, 2009), and is often mistakenly perceived as a safe and even beneficial drug, making it a particular concern for women of reproductive age (Sessa B & Nutt D, 2015).

Several aspects of MDMA use may be particularly harmful during pregnancy and could negatively affect fetal outcomes. Maternal appetite suppression, sleep difficulties, increased heart rate and body temperature, depressive symptoms, and neurohormonal alterations, especially high cortisol levels associated with MDMA use (Parrott AC, Montgomery C et al., 2014), have all been demonstrated to have detrimental effects on the fetus. Women are also significantly more at risk of developing hyponatremia following acute MDMA use, especially when it is taken at dance clubs or raves (van Dijken GD, Blom RE, Hene RJ, Boer WH, & NIGRAM Consortium, 2013). Moreover, reductions in maternal serotonin levels caused by MDMA use may directly adversely affect fetal development as serotonin is involved in control of morphogenesis both before and after the appearance of serotonergic neurons (Cote F et al., 2007).

MDMA has been demonstrated to cross the placenta in pregnant rats (Campbell NG, Koprich JB, Kanaan NM, & Lipton JW, 2006) with correspondent levels in the fetal brain. Preclinical studies (Skelton MR, Williams MT, & Vorhees CV, 2008) suggest that fetal exposure to MDMA in the third trimester can affect locomotor activity levels and alter risk taking behavior and spatial learning (Thompson VB et al., 2009). Neonatal exposure in rat models, for example, produced impaired path integration learning (Vorhees CV, Reed TM, Skelton MR, & Williams MT, 2004) possibly through changes in the release of dopamine and serotonin in the striatum and hippocampus (Galineau L et al., 2005). MDMA treatment prenatally of pregnant rats led to reduced bodyweight and reduced learning of motor skills in adulthood (Adori C et al., 2010), and growth retardation and poorer motor skills in BALB/C mice pups. MDMA exposure in 6 day old rat pups also facilitated neuronal death in cortical, thalamic, and hypothalamic brain regions (Dzietko M et al., 2010), as had been shown previously by Meyer (Meyer JS, Grande M, Johnson K, & Ali SF, 2004).

Pregnancy outcomes after MDMA use have been examined in only a few studies. In a retrospective study in the U.K., prenatal MDMA exposure was associated with an increase in congenital defects and cardiovascular anomalies (McElhatton PR, Bateman DN, Evans C, Pughe KR, & Thomas SH, 1999). Similar cardiac malformations as well as spontaneous abortions were noted in another study in the Netherlands (van Tonningen-van Driel MM, Garbis-Berkvens JM, & Reuvers-Lodewijks WE, 1999). Our small prospective, controlled study of pregnant women who used MDMA primarily in the first and second trimesters found no effects on fetal growth outcomes, but there were differences in sex ratio, with more males in the MDMA group. One infant in the MDMA-exposed group was born with Townes-Brooks Syndrome (Singer LT et al., 2012a). When the same cohort was followed over the first year of life, motor delays were seen at four months and persisted to 12 months of age. MDMA-exposed infants were delayed in standing and walking progressions as well as in mental development, with a dose-response relationship of heavier exposure predicting greater delay, after control for confounding variables (Singer LT et al., 2012b). At 24

months, the heavier group also had motor deficits compared to light and non-exposed children (Singer LT et al., 2015).

Little is known about patterns of use, and the demographics of women who use MDMA during pregnancy. Ho et al, 2001 (Ho E, Karimi-Tabesh L, & Koren G, 2001) reported on a prospective observational study of 132 pregnant MDMA using women who contacted a risk assessment program and were compared to callers who did not use MDMA. MDMA users reported greater use of tobacco, alcohol, cocaine, and other illicit drugs than non-users and were more likely to be unmarried with psychiatric problems. However, in our U.K. study of pregnancy and infant outcomes reported above, MDMA users were not different from non-users in sociodemographic characteristics but they were similar to Ho's study in that they were higher users of alcohol and several other illicit drugs (Moore DG et al., 2010).

The present study extends our prior findings by follow-up of this U.K. cohort beyond 12 months to two years of age and by using longitudinal analyses to assess the effects of MDMA over time, while also assessing the effects of other drugs, maternal psychological distress, gender, and the quality of the home environment on the trajectory of mental and motor developmental outcomes.

2. Methods

2.1 Participants

Methods and Procedures from this study have been reported previously (Moore DG et al., 2010; Moore DG et al., 2011; Singer LT et al., 2012a; Singer LT et al., 2012b; Singer LT et al., 2015), but will be reviewed here. Prospective recruitment of all mothers and infants was conducted through the Case Western Reserve University (CWRU) and University of East London (UEL) Drugs and Infancy Study (DAISY) that focused on recreational drug use in pregnant women (Moore DG et al., 2010; Moore DG et al., 2011). Recruitment was implemented through either referral by midwives, response to leaflets describing the study distributed at prenatal clinics, or advertisements in pregnancy magazines. Study description requested participation of pregnant women who had used recreational drugs during pregnancy such as ecstasy, tobacco, cannabis, alcohol, and cocaine were asked to participate. Exclusionary factors included maternal/child HIV positive status, maternal moderate/severe intellectual disability or severe psychiatric or medical illness; or, for the child, other major medical illnesses. All participants were informed that their data would remain confidential and gave informed written consent under protocols approved by university (CWRU and UEL) and National Health Service (UK) ethics committees.

Of 126 women initially recruited, five did not meet study criteria, and 25 did not come to the first visit of 96 subjects enrolled and seen for infant 82 (85%) infants were seen at one month, 87 (91%) at four months, 79 (82%) at 12 months, 67 (70%) at 18, and 66 (69%) at 24 months. Over the two year period, 93 children (25 MDMA (12 lighter, 13 heavier), 68 non-MDMA) had at least one Bayley assessment with 87% (n = 81) two assessments. The three mothers whose babies were not assessed were lighter MDMA users. Attrition did differ by group (whether MDMA was defined as yes vs no, or none, light, or heavy). Those lost to follow-up at 24 month assessments were more likely to have lower family income and lower

WASI Block Design and Similarities scores. They did not differ in maternal age, race/ethnicity, education, parity, psychological distress (GSI), DAST scores, amount of substances used during pregnancy, infant birth outcomes (gestational age, weight, length, head circumference), or gender.

2.2 Measures of MDMA Exposure and Covariates

Maternal interviews were conducted by trained research assistants either in parents' homes, at the UEL laboratory, or by telephone. Interviews occurred over the course of their pregnancy on three separate occasions, but if needed, a combined set of interviews was given on one occasion if enrollment was late in the pregnancy (Moore DG et al., 2010). Sixty two women completed the interview during pregnancy, with 24 interviewed postnatally.

2.3 Prenatal Levels of Drug Exposure

The interview was an adaptation of the Maternal Post-Partum Interview used in prior U.S. studies of alcohol and cocaine exposure (Singer LT et al., 2002). Women were requested to describe their intake of substances commonly used in UK cohorts based on prior UEL drug questionnaires (Parrott AC, Milani RM, Parmar R, & Turner JD, 2001). Part 1 requested information about total lifetime drug use and use during the year leading up to conception. Part 2 asked about drug use in the month prior to pregnancy and over the first two trimesters, and Part 3 asked about use in the last trimester. For each section, values were computed for tobacco/cigarettes (#), alcohol (# units) (10 ml in the U.K.), marijuana joints/cigarettes (#), MDMA tablets (#), heroin, cigarettes or injections (#), ketamine (grams), crack (# rocks) or cocaine (# lines), benzodiazepine and LSD tablets (#), and hallucinogenic mushrooms (#). Frequency of use for each drug was recorded on a scale ranging from zero (none) to seven (daily use). An average dose per week for each drug was calculated by multiplying the frequency by the amount taken per occasion.

Users were women that self-admitted to MDMA use at any time during pregnancy or in the month prior to pregnancy. Women who had used prior to this time point but reported no use during pregnancy ($n = 32$) or who had never used were classified as non-users, since we were interested in the outcome of fetal exposure. Users were divided into heavier ($n = 13$) and lighter ($n = 15$) groups based on a median split for the amount of MDMA taken averaged over the pregnancy (median = 0.14). Heavier users averaged $3.3 (\pm 4)$ tablets in the month prior to pregnancy compared to $.12 \pm .2$ tablets for lighter users (Wilcoxin test $p < .007$); 1.6 ± 2 vs. $.12 \pm 1$ tablets in the first trimester ($p < .12$), and $.15 \pm .6$ vs. $.02 \pm .1$ in the second trimester, $p > .20$. Since only one mother reported using MDMA in the third trimester, we also calculated means excluding the third trimester for heavier and lighter users to reflect actual exposure. Excluding the third trimester, heavier users averaged 1.7 ± 1.8 tablets per week ($R = .22-.6.0$) and lighter users averaged $.09 \pm .06$ tablets per week ($R = .02-.19$).

The initial interview also obtained information for each drug on age at first use, age when drug use was discontinued, and typical and highest consumption (Singer LT et al., 2012a).

2.4 Maternal Drug Use, Demographics, and Psychological Measures

The Drug Abuse Screening Test (DAST) (Skinner HA, 1982) was given at first interview to characterize level of drug dependence. The DAST yields a quantitative index of the degree of problems related to drug use, with a cutoff score of 16 (out of 20) indicating a severe level of secondary problems in life areas of marital and social relations, and employment, legal, physical, and medical problems.

At each visit, the Brief Symptom Inventory (BSI) (Derogatis LR, 1992), a widely used self-report, 53 item questionnaire was also given to describe experience of a range of psychiatric symptom patterns. The BSI yields 9 subscales (somatic complaints, obsessive compulsive behavior, interpersonal sensitivity, depression, anxiety, phobic anxiety, paranoid ideation, hostility and psychoticism) that possess consensually valid clinical significance. A summary score, the General Severity Index (GSI), measures overall psychological distress. Cut off scores identify subjects whose symptoms reach severity levels suggestive of the need for clinical intervention, i.e. > the 84th percentile (moderate) or > the 98th percentile (severe) compared to same sex, non-patient norms. BSI data from the one month visit were used because initial differences between MDMA and non-MDMA groups declined over time (Turner JJ et al., 2014).

Data on maternal age at infant birth, marital status, ethnicity, educational level, and household income were obtained. After infant birth, fetal growth measurements (weight, length, head circumference, and gestational age) and health information were taken from hospital records. Women were also administered two subsets of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler D, 1999), a standardized IQ test, i.e. the Block Design, and the Similarities Scales. Each scale yields a t score with a mean of 50 and a standard deviation of 8. At each visit, the Home Observational Measure of the Environment (HOME) was administered in interview format to measure the quality of the caregiving environment (Caldwell Bettye M & Bradley Robert H, 1984).

2.5 Infant Developmental Outcomes

The Bayley Scales of Infant Development III (Bayley N, 1993) are standardized assessments of infant development that were administered at four, 12, 18, and 24 months of age. The Mental Scale yields a Mental Development Index (MDI), a standard score reflecting memory, language, and problem solving abilities. The Psychomotor Index (PDI) measures gross and fine motor control and coordination. Normative data from the scales yield a mean of 100 and standard deviation of 15. The Behavioral Rating Scale (BRS) assesses quality of infant performance across several developmental domains based on the assessor's observations. Domains include orientation/engagement, emotional regulation, and motor quality at all ages, and attention/arousal, which is measured at 4 months of age only. Motor quality considers the overall quality of muscle tone and fine and gross motor movements. Percentile scores are derived from the total raw and factor scores. BRS scores can be categorized as within normal limits, questionable, and non-optimal. All assessors were master's level psychology assistants or the equivalent who were masked to infant drug exposure.

3. Statistical Analyses

Descriptive statistics were used to compare sample characteristics of three MDMA groups. The effects of MDMA (heavy, light, none) on MDI, PDI, and two subscales of the BRS (emotional regulation and orientation) were evaluated using a repeated measures mixed model approach with a random intercept. An unstructured covariance matrix was used to account for correlated responses within a subject. Percentile scores for the BRS motor quality subscale were dichotomized at 75% due to its skewed distribution, which was tested using repeated measure mixed logistic models also with a random intercept and an unstructured covariance matrix. The actual age of the child was used instead of assessment wave to better capture variability and trends over time. Due to a possible curvilinear relationship between outcomes and test age, a quadratic term [age (2)] was evaluated. We tested the homogeneity of MDMA effects, as well as the effects of gender and other covariates on infant development over time by including an interaction term with test age. If the interaction was significant at $p < .10$, the interaction terms were included in the model. Missing data were modeled using full-information maximum likelihood, which utilizes all available information from the observed data. Since the Attention/Arousal factor was assessed only at 4 months, multiple linear regression was used for that variable.

Covariates that differed by MDMA status at $p < .2$ and were associated with the given outcome at $p < .2$ for at least two time points were evaluated in the multivariable model stepwise and retained if, on entry, they were significant at $p < .10$ or caused substantial change ($> 10\%$) in the MDMA coefficient. Adjusted least squares mean (M_{adj}) and standard errors (SE) were calculated from the models. MDMA status by gender interactions were also evaluated.

4. Results

4.1 Maternal Demographics and Drug use

Table 1 reports demographic, medical, and psychological characteristics of women who used MDMA (heavier and lighter groups) vs. women who did not use MDMA while pregnant and their pregnancy outcomes. As reported previously (Singer LT et al., 2012a; Singer LT et al., 2012b) the maternal sample was primarily white; married or with a partner; with some university education; came from a full range of socioeconomic (SES) classes, with many from middle and high SES backgrounds; and were overall in the average range of intellectual ability. MDMA using women had fewer children. Overall prenatal drug use and the negative sequelae of drug use as measured by the DAST were different among the groups (Table 1). Women who used MDMA during pregnancy had higher scores on the DAST, indicating greater severity of sequelae related to their drug use. However, the mean scores were below clinical significance for both groups, with $< 5\%$ for each group scoring above the cutoff of 16. All births were singleton births. Child birth outcomes (Table 1) did not differ by group in gestation period, birthweight, prematurity, length, or head circumference although this finding is inconclusive for birth length and head circumference due to missing data. As reported previously (Singer LT et al., 2012a), however, MDMA-exposed infants were significantly more likely to be male (71% vs. 46%). This remained the

case even after controlling for other drug use differences with the O.R. of having a male birth after MDMA exposure = 3.2, (95% CI: 1.2–8.2, $p < .02$).

Because one child in the MDMA-exposed group was diagnosed with Townes-Brocks Syndrome, a rare genetic autosomal dominant multiple malformation of the gene *SALL1* (Powell CM & Michaelis RC, 1999), all outcome analyses with significant findings were rerun excluding this child and results did not differ. Thus, the presented findings include all in the MDMA-exposed group (Singer LT et al., 2012a).

Table 2 describes the group average and median drug use during pregnancy for the three groups across the full range of substances reported. MDMA users were more likely to use marijuana, cocaine, LSD, and mushrooms during their pregnancy. There were few overall differences.

4.2 Models

We tested the main effects of and the interactions of level of MDMA prenatal exposure and infant test age on BSID III measures over time (Table 3). There was a significant effect of level of MDMA exposure on PDI over time ($F = 6.90$, $p < .002$), adjusted for child gender, test age, test age (2), gender x child test age, parity and amount of prenatal cocaine exposure. Children with heavier exposure had on average an 11-point deficit in PDI compared with lighter exposed children and a 6-point deficit compared to non-exposed children over the first two years of life (Figure 1). There was no effect of MDMA exposure on the MDI ($F = 1.28$, $p < .29$) adjusted for child test age, the HOME score at 12 months, child gender, and gender x child test age. There were significant effects of exposure on BRS motor quality, adjusted for test age, child gender, and the HOME score. Children with heavier MDMA exposure were twice as likely to be rated by examiners as demonstrating poorer motor quality ($OR = 2.19$, 95%CI= 1.02–4.70, $p < .045$) than lighter and non-exposed children.

The Attention/Arousal subdomain of the BRS was measured only at 4 months. Heavier MDMA-exposed infants were perceived as having poorer attentional skills than lighter exposed infants ($p < .001$) and there was a non-significant trend for them to perform more poorly than non-exposed infants ($p < .10$) (See Table 3). There were no reliable effects on BRS orientation or emotional regulation. No test age by MDMA interaction was found, indicating that the effects of MDMA on the outcomes did not significantly vary over the first two years of life.

Covariate Effects—Covariate effects were found for the HOME measure and gender. Although boys had higher scores on the MDI and PDI than girls at baseline assessment (Table 3), there were significant gender by age interactions that resulted in boys performing worse than girls as they got older. The mean MDI at 24 months was 95.58 (SE = 1.81) for boys vs. 106.44 (SE = 1.90) for girls, while PDI at 24 months was 93.24 (SE = 1.65) for boys vs. 101.81 (SE = 1.92) for girls. Higher quality of the home environment was also a predictor of a higher MDI score and better emotional regulation and motor quality over time as rated by examiners. Adverse effects of prenatal alcohol exposure on motor development, seen at 4 months, were not a significant factor on the overall trajectory of the PDI.

5. Discussion

In this longitudinal study, infants whose mothers self-reported heavier MDMA use in the month prior to and during pregnancy had persistent motor delays from 4 months to two years of age. The effects of MDMA could not be attributed to other drug or alcohol exposures nor to sociodemographic factors. Motor skill deficits/delays had been apparent as early as four months of age (Singer LT et al., 2012a) and also at 12 months, when the heavier MDMA-exposed cohort exhibited deficits in standing and walking progressions compared to non-exposed infants (Singer LT et al., 2012b). Thus, the current study indicates a pervasive and continuing deficit in motor skills over the first 2 years of life compared to lighter and non-exposed children.

There were no effects on MDI. Prior effects of MDMA on MDI seen at 12 months were no longer significant once the overall trajectory of development was considered.

MDMA affects the serotonin (5-HT) neurotransmitter that plays a key role in regulating brain development (Bonnin A & Levitt P, 2011). MDMA also increases cortisol levels in adult users, which may have indirect effects on fetal serotonergic activity (Parrott AC, Moore DG et al., 2014). There are no other human studies of the developmental outcomes of infants exposed to MDMA for comparison.

Our findings are consistent with a number of preclinical studies. Increases in dopaminergic fibers in areas critical to attention, reward, and motor behavior have been noted (Thompson VB et al., 2012) after MDMA exposure. Adori et al (Adori C et al., 2010) found that intermittent MDMA exposure with a low cumulative dose early in gestation such as in this sample was related to reduced muscle strength and reduced motor skill learning of offspring in adulthood. Similarly, decreased motor function in exposed mouse pups has been noted by Kaizaki (Kaizaki A, Tanaka S, Yoshida T, & Numazawa S, 2014).

Although there are no comparable human studies of MDMA exposure, after prenatal exposure to methamphetamine, a similar amphetamine type drug, Smith et al (Smith LM et al., 2015) found that methamphetamine-exposed infants demonstrated motor deficits relative to comparison infants. Specifically, they identified poorer quality of movement in the neonatal period, and decreased grasping skill with heavier exposure at 1 and 3 years (Smith LM et al., 2015).

There are a number of potential mechanisms for MDMA effects on motor development. The neurotransmitter serotonin is a particular target of MDMA and maternal depletion of serotonin during pregnancy may have adverse effects on the development of the fetal brain, particularly in motor development (Jacobs BL & Fornal CA, 1995; Wurtman RJ, 2005)

Although the sample size of the present study is small, the homogeneity of the sample, primarily middle-class, employed, married, and without significant social problems associated with drug use, enhances confidence in the findings, as does the study's prospective, longitudinal design, the measurement and control of a large number of confounding variables, and the voluntary recruitment of the sample. The small sample size of heavier users precluded evaluating drug interaction effects, which may be important, as

simultaneous use of MDMA and alcohol is prevalent, as in this sample, and has been demonstrated to have gender specific effects on exploratory behavior and working memory in preclinical studies (Canales JJ & Ferrer-Donato A, 2014). Additional limitations include the lack of confirming biomarkers, absence of data on paternal drug use and possible sampling bias associated with volunteers.

6. Conclusion

Despite these limitations, the deficits in motor skills identified early in infancy and persisting until two years of age associated with heavier MDMA prenatal exposure are of significant concern. Most women in this study discontinued MDMA use after the first trimester, indicating that alterations occurred early in fetal development. Discontinuance of use after the first trimester (Moore DG et al., 2010), also suggests unplanned pregnancy. MDMA use has been associated with raised libido and sexual risk-taking at higher doses, including unprotected sex (McElrath K, 2005; Topp L, Hando J, & Dillon P, 1999). Given the extensive global recreational use of MDMA, women of child bearing age should be cautioned about possible harm to the fetus. Further studies are needed to confirm these findings as well as to determine if there are long-term effects of exposure.

Acknowledgments

Thanks are extended to the participating families and hospitals; to Terri Lotz-Ganley for manuscript preparation; and to Teresa Linares, Ph.D., Paul Weishampel, M.A., Diana Fox, L.S.W., Ishan Roy, B.S. (Case Western Reserve University), Fleur Braddick, Emma Axelsson, Stephanie Lynch, Helena Ribeiro, and Caroline Frostick (University of East London), for data collection, coding, and analytic assistance.

Funding/Support:

Supported by grant DA14910-05 NIH — National Institute on Drug Abuse. The National Institute on Drug Abuse had no role in the study design; collection, analysis and interpretation of data, in the writing of the report, nor in the decision to submit the paper for publication.

Portions of this paper were presented at the 2nd Conference on Novel Psychoactive Substances, Swansea, Wales, United Kingdom, September 12–13, 2013 and at the Neurobehavioral Teratology Society Meetings in Tucson, Arizona, June 25, 2013.

The authors have indicated they have no financial relationships relevant to this article to disclose.

References

- Adori C, Zelena D, Timar J, Gyarmati Z, Domokos A, Sobor M, et al. Intermittent prenatal MDMA exposure alters physiological but not mood related parameters in adult rat offspring. *Behavioural Brain Research*. 2010; 206(2):299–309.10.1016/j.bbr.2009.09.031 [PubMed: 19782105]
- Bayley, N. Bayley scales of infant development: Manual. New York, NY: Psychological Corp; 1993.
- Bonnin A, Levitt P. Fetal, maternal, and placental sources of serotonin and new implications for developmental programming of the brain. *Neuroscience*. 2011; 197:1–7.10.1016/j.neuroscience.2011.10.005 [PubMed: 22001683]
- Caldwell Bettye, M.; Bradley Robert, H. Administration manual: HOME observation for measurement of the environment. Little Rock, Ark: University of Arkansas at Little Rock, Center for Child Development and Education; 1984.
- Campbell NG, Koprich JB, Kanaan NM, Lipton JW. MDMA administration to pregnant sprague-dawley rats results in its passage to the fetal compartment. *Neurotoxicol Teratol*. 2006; 28(4):459–465. S0892-0362(06)00074-2 [pii]. [PubMed: 16905291]

- Canales JJ, Ferrer-Donato A. Prenatal exposure to alcohol and 3,4-methylenedioxymethamphetamine (ecstasy) alters adult hippocampal neurogenesis and causes enduring memory deficits. *Developmental Neuroscience*. 2014; 36(1):10–17.10.1159/000356820 [PubMed: 24457993]
- Chabrol H. MDMA assisted psychotherapy found to have a large effect for chronic post-traumatic stress disorder. *Journal of Psychopharmacology*. 2013; 27(9):865–866.10.1177/0269881113495119 [PubMed: 23981728]
- Cote F, Fligny C, Bayard E, Launay JM, Gershon MD, Mallet J, et al. Maternal serotonin is crucial for murine embryonic development. *Proceedings of the National Academy of Sciences of the United States of America*. 2007; 104(1):329–334. 0606722104 [pii]. [PubMed: 17182745]
- Derogatis, LR. The brief symptom inventory (BSI): Administration, scoring & procedures manual-II. Towson, MD: Clinical Psychometric Research; 1992.
- Dzietko M, Sifringer M, Klaus J, Endesfelder S, Brait D, Hansen HH, et al. Neurotoxic effects of MDMA (ecstasy) on the developing rodent brain. *Developmental Neuroscience*. 2010; 32(3):197–207.10.1159/000313473 [PubMed: 20616555]
- Galineau L, Belzung C, Kudas E, Bodard S, Guilloteau D, Chalon S. Prenatal 3,4-methylenedioxymethamphetamine (ecstasy) exposure induces long-term alterations in the dopaminergic and serotonergic functions in the rat. *Brain Res Dev Brain Res*. 2005; 154(2):165–176. S0165-3806(04)00338-4. [PubMed: 15707670]
- Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *Pharmacol Rev*. 2003; 55(3):463–508. [PubMed: 12869661]
- Greer G, Tolbert R. Subjective reports of the effects of MDMA in a clinical setting. *Journal of Psychoactive Drugs*. 1986; 18(4):10.1080/02791072.1986.10472364
- Ho E, Karimi-Tabesh L, Koren G. Characteristics of pregnant women who use ecstasy (3, 4-methylenedioxymethamphetamine). *Neurotoxicology and Teratology*. 2001; 23(6):561–567. S0892036201001787. [PubMed: 11792525]
- Jacobs, BL.; Fornal, CA. Serotonin and behaviour: A general hypothesis. In: Bloom, KDFE., editor. *Psychopharmacology*. New York: Raven Press Ltd; 1995. p. 461-469.
- Kaizaki A, Tanaka S, Yoshida T, Numazawa S. Maternal MDMA administration in mice leads to neonatal growth delay. *The Journal of Toxicological Sciences*. 2014; 39(1):33–39. DN/JST.JSTAGE/jts/39.33 [pii]. [PubMed: 24418707]
- Kirkpatrick MG, Lee R, Wardle MC, Jacob S, de Wit H. Effects of MDMA and intranasal oxytocin on social and emotional processing. *Neuropsychopharmacology*. 2014; 39(7):1654–1663.10.1038/npp.2014.12 [PubMed: 24448644]
- McElhatton PR, Bateman DN, Evans C, Pughe KR, Thomas SH. Congenital anomalies after prenatal ecstasy exposure. *Lancet*. 1999; 354(9188):1441–1442. S014067369902423X. [PubMed: 10543673]
- McElrath K. MDMA and sexual behavior: Ecstasy users' perceptions about sexuality and sexual risk. *Substance use & Misuse*. 2005; 40(9–10):1461–1477. H41661U463L32853. [PubMed: 16048828]
- Meyer JS, Grande M, Johnson K, Ali SF. Neurotoxic effects of MDMA ("ecstasy") administration to neonatal rats. *International Journal of Developmental Neuroscience*. 2004; 22(5–6):261–271.10.1016/j.ijdevneu.2004.04.007 [PubMed: 15380826]
- Mohan, J., editor. *World drug report 2014*. Vienna, Austria: United Nations Office on Drugs and Crime; Jun. 2014 p. 2p. 3p. 123-152.
- Moore DG, Turner JD, Parrott AC, Goodwin JE, Fulton SE, Min MO, et al. During pregnancy, recreational drug-using women stop taking ecstasy (3,4-methylenedioxy-N-methylamphetamine) and reduce alcohol consumption, but continue to smoke tobacco and cannabis: Initial findings from the development and infancy study. *J Psychopharmacol*. 2010; 24(9):1403–1410.10.1177/0269881109348165 [PubMed: 19939863]
- Moore DG, Turner JJD, Goodwin JE, Fulton SE, Singer LT, Parrott AC. In utero exposure to the popular 'recreational' drugs MDMA (ecstasy) and methamphetamine (ice, crystal): Preliminary findings. *Clin Dev Med*. 2011; 188:169–182.
- Parrott AC. MDMA (3,4-methylenedioxymethamphetamine) or ecstasy: The neuropsychobiological implications of taking it at dances and raves. *Neuropsychobiol*. 2004; 50(4):329–335.

- Parrott AC. MDMA, serotonergic neurotoxicity, and the diverse functional deficits of recreational 'ecstasy' users. *Neuroscience and Biobehavioral Reviews*. 2013; 37(8):1466–1484.10.1016/j.neubiorev.2013.04.016 [PubMed: 23660456]
- Parrott AC, Milani RM, Parmar R, Turner JD. Recreational ecstasy/MDMA and other drug users from the UK and Italy: Psychiatric symptoms and psychobiological problems. *Psychopharmacology*. 2001; 159(1):77–82.10.1007/s002130100897 [PubMed: 11797073]
- Parrott AC, Montgomery C, Wetherell MA, Downey LA, Stough C, Scholey AB. MDMA, cortisol, and heightened stress in recreational ecstasy users. *Behavioural Pharmacology*. 2014; 25(5–6): 458–472.10.1097/FBP.000000000000060 [PubMed: 25014666]
- Parrott AC, Moore DG, Turner JJD, Goodwin J, Min MO, Singer LT. MDMA and heightened cortisol: A neurohormonal perspective on the pregnancy outcomes of mothers used 'ecstasy' during pregnancy. *Hum Psychopharmacol Human Psychopharmacology*. 2014; 29(1):1–7. [PubMed: 24424703]
- Powell CM, Michaelis RC. Townes-brooks syndrome. *J Med Genet*. 1999; 36(9902)
- Ricaurte GA, Yuan J, McCann UD. (+/-)3,4-methylenedioxymethamphetamine ('ecstasy')-induced serotonin neurotoxicity: Studies in animals. *Neuropsychobiology*. 2000; 42(1):5–10. 26664 [pii]. [PubMed: 10867550]
- SAMHSA Center for Behavioral Health Statistics and Quality. Results from the 2012 national survey on drug use and health: Summary of national findings. United States of America: 2013.
- Sessa B. Could MDMA be useful in the treatment of post-traumatic stress disorder? *Progress in Neurology and Psychiatry*. 2011; 15(6):4–7.
- Sessa B, Nutt D. Making a medicine out of MDMA. *The British Journal of Psychiatry*. 2015; 206(1): 4–6.10.1192/bjp.bp.114.152751 [PubMed: 25561485]
- Singer LT, Arendt R, Minnes S, Farkas K, Salvator A, Kirchner HL, et al. Cognitive and motor outcomes of cocaine-exposed infants. *JAMA*. 2002; 287(15):1952–1960. [PubMed: 11960537]
- Singer LT, Moore DG, Fulton S, Goodwin J, Turner JJD, Min MO, et al. Neurobehavioral outcomes of infants exposed to MDMA (ecstasy) and other recreational drugs during pregnancy. *Neurotoxicol Teratol*. 2012a; 34(3):303–310.10.1016/j.ntt.2012.02.001 [PubMed: 22387807]
- Singer LT, Moore DG, Min MO, Goodwin J, Turner JJ, Fulton S, Parrott AC. Developmental outcomes of 3, 4-methylenedioxymethamphetamine (ecstasy)-exposed infants in the UK. *Human Psychopharmacology: Clinical and Experimental, Special Edition*. 2015; 30(4):290–294.10.1002/hup.2459
- Singer LT, Moore DG, Min MO, Goodwin J, Turner JJD, Fulton S, et al. One-year outcomes of prenatal exposure to MDMA and other recreational drugs. *Pediatrics*. 2012b; 130(3):407–413.10.1542/peds.2012-0666 [PubMed: 22908109]
- Skelton MR, Williams MT, Vorhees CV. Developmental effects of 3,4-methylenedioxymethamphetamine: A review. *Behav Pharmacol*. 2008; 19:91–111.10.1097/FBP.0b013e3282f62c76 [PubMed: 18332674]
- Skinner, HA. Drug use questionnaire (DAST-20). Toronto, Canada: Addiction Research Foundation of Ontario; 1982.
- Smith LM, Diaz S, LaGasse LL, Woudes T, Derauf C, Newman E, et al. Developmental and behavioral consequences of prenatal methamphetamine exposure: A review of the infant development, environment, and lifestyle (IDEAL) study. *Neurotoxicology and Teratology*. 2015; 51:35–44.10.1016/j.ntt.2015.07.006 [PubMed: 26212684]
- Thompson VB, Heiman J, Chambers JB, Benoit SC, Buesing WR, Norman MK, ... Lipton JW. Long-term behavioral consequences of prenatal MDMA exposure. *Physiology & Behavior*. 2009; 96(4–5):593–601.10.1016/j.physbeh.2008.12.013 [PubMed: 19162054]
- Thompson VB, Koprach JB, Chen EY, Kordower JH, Terpstra BT, Lipton JW. Prenatal exposure to MDMA alters noradrenergic neurodevelopment in the rat. *Neurotoxicology and Teratology*. 2012; 34(1):206–213.10.1016/j.ntt.2011.09.005 [PubMed: 21978916]
- Topp L, Hando J, Dillon P. Sexual behaviour of ecstasy users in Sydney, Australia. *Cult Health Sex*. 1999; 1(2):147–159.
- Turner JJ, Parrott AC, Goodwin J, Moore DG, Fulton S, Min MO, et al. Psychiatric profiles of mothers who take ecstasy/MDMA during pregnancy: Reduced depression 1 year after giving birth and

- quitting ecstasy. *J Psychopharmacol.* 2014; 28(1):55–61.10.1177/0269881113515061 [PubMed: 24327452]
- van Dijken GD, Blom RE, Hene RJ, Boer WH. NIGRAM Consortium. High incidence of mild hyponatraemia in females using ecstasy at a rave party. *Nephrology, Dialysis, Transplantation.* 2013; 28(9):2277–2283.10.1093/ndt/gft023
- van Tonningen-van Driel MM, Garbis-Berkvens JM, Reuvers-Lodewijks WE. Pregnancy outcome after ecstasy use; 43 cases followed by the teratology information service of the national institute for public health and environment (RIVM) [Zwangerschapsuitkomst na ecstasygebruik; 43 gevallen gevolgd door de Teratologie Informatie Service van het RIVM]. *Nederlands Tijdschrift Voor Geneeskunde.* 1999; 143(1):27–31. [PubMed: 10086095]
- Vorhees CV, Reed TM, Skelton MR, Williams MT. Exposure to 3, 4-methylenedioxymethamphetamine (MDMA) on postnatal days 11–20 induces reference but not working memory deficits in the morris water maze in rats: Implications of prior learning. *International Journal of Developmental Neuroscience : The Official Journal of the International Society for Developmental Neuroscience.* 2004; 22(5–6)
- Wechsler, D. Wechsler abbreviated scale of intelligence: WASI. San Antonio, TX: Psychological Corp., Harcourt Brace; 1999.
- Wu LT, Parrott AC, Ringwalt CL, Yang C, Blazer DG. The variety of ecstasy/MDMA users: Results from the national epidemiologic survey on alcohol and related conditions. *The American Journal on Addictions /American Academy of Psychiatrists in Alcoholism and Addictions.* 2009; 18(6): 452–461.10.3109/10550490903206049 [PubMed: 19874166]
- Wurtman RJ. Genes, stress, and depression. *Metabolism: Clinical and Experimental.* 2005; 54(5 Suppl 1):16–19. S0026049505000296 [pii]. [PubMed: 15877307]

Highlights

- Recreational use of 3,4 methylenedioxymethamphetamine (Ecstasy, MDMA) is increasing worldwide.
- Reductions in maternal serotonin levels caused by MDMA use may adversely affect fetal development.
- In this longitudinal study, higher levels of maternal MDMA use prenatally predicted poorer motor development from 4–24 months of age.
- Women of childbearing age should be cautioned about use of MDMA during pregnancy.

Figure 1.

Estimated Means of Bayley Psychomotor Development Index by level of MDMA exposure at each assessment age, adjusted for age², infant gender, interaction of infant gender and assessment age, parity, and prenatal cocaine exposure. Heavier group differs from None ($p < .05$) and from Lighter group ($p < .001$).

Table 1

Sample Characteristics at Birth by Heavier, Lighter, and Non-MDMA Exposure (N=93)

	MDMA Status			p
	Heavier (n=13)	Lighter (n=12)	None (n=68)	
<i>Maternal Characteristics</i>				
White, <i>n</i> (%)	12 (92)	10 (83)	51 (75)	.35
Registered Disabled, <i>n</i> (%)	0	0	5 (8)	.40
Married/with partner, <i>n</i> (%)	10 (77)	9 (75)	57 (84)	.68
Family Income, <i>n</i> (%)				.51
<10K British Pounds	0	4 (33)	13 (19)	
10–40K British Pounds	9 (69)	6 (50)	40 (59)	
>40K British Pounds	4 (31)	2 (17)	15 (22)	
Maternal age at birth, M (SD)	26.8 (6.9)	29.5 (5.3)	30.3 (6.4)	.21
Maternal education, M (SD)	15.0 (2.5)	15.5 (3.2)	14.9 (2.9)	.84
WASI Block Design, M (SD) ^d	55.6 (9.48)	60.0 (5.32)	56.0 (9.5)	.50
WASI Similarities, M (SD)	48.1 (8.0)	56.3 (7.8)	49.4 (8.9)	.09
Parity, M (SD)	1.15 (.37)	1.25 (.45)	1.88 (1.11)	.01 ^a
GSI at birth, M (SD) ^e	.72 (.89)	.86 (.82)	.54 (.56)	.31
DAST score, M (SD) ^f	7.4 (4.3)	7.8 (3.5)	4.6 (4.4)	.02 ^b
HOME score at 12 month, M (SD) ^g	40.4 (3.36)	39.9 (3.09)	39.6 (3.42)	.73
<i>Child Characteristics</i>				
White, <i>n</i> (%)	10 (77)	9 (75)	51 (75)	.99
Male, <i>n</i> (%)	8 (62)	10 (83)	31 (46)	.04 ^c
Special Baby Care Unit, <i>n</i> (%)	1 (8)	1 (8)	8 (12)	.86
Gestation, weeks, M (SD)	40.1 (1.21)	40.1 (2.11)	39.5 (1.5)	.30
Preterm (< 37 Weeks), <i>n</i> (%)	0	1 (8.3)	1 (1.5)	.27
Birth Weight (g), M (SD)	3537 (522)	3513 (553)	3344 (511)	.34
Birth Length (cm), M (SD)	52.9 (1.55)	50.6 (2.88)	51.4 (2.70)	.44
Head Circumference (cm), M (SD)	34.1 (1.90)	35.7 (1.83)	34.3 (1.90)	.20

^aSignificant post-hoc (p <.05) difference with Tukey correction between Heavier group vs. None^bNo significant post-hoc group difference^cSignificant difference between MDMA exposed group vs. None^dWechsler Abbreviated Scale of Intelligence^eGeneral Severity Index^fDrug Abuse Screening Test^gHome Observational Measure of the Environment

Table 2

Maternal Drug Use During Pregnancy by Heavier, Lighter, and Non-MDMA Exposure^a

	MDMA Status						p
	Heavier (n=13)			Lighter (n=15)			
Drug, per week	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	
Cigarettes	50.2 (39.9)	45.0 (0–118)	23.8 (36.8)	9.6 (0–123)	32.5 (49.1)	13.19 (0–280)	.10
Alcohol, units	12.5 (16.0)	4.9 (.06–51)	6.06 (4.52)	5.25 (0–14.7)	6.6 (12.9)	2.3 (0–84)	.12
Marijuana, joints	9.9 (24.2)	.25 (0–87.5)	9.51 (14.79)	3.40 (.01–3.4)	6.3 (15.0)	0.06 (0–88)	.04
MDMA, tablets	1.3 (1.4)	.75 (.17–4.5)	.07 (.04)	.06 (.01–.14)	--	--	--
Cocaine, doses	.15 (.28)	.05 (0–1.0)	.24 (.64)	.005 (0–2.4)	.02 (0.1)	0 (0–8)	.0001 ^b
Crack, rocks	.04 (.11)	0 (0–.37)	.01 (.04)	0 (0–.17)	1.0 (5.0)	0 (0–38)	.81
Amphetamine, doses	.03 (.10)	0 (0–.33)	.05 (.14)	0 (0–.52)	.0003 (.001)	0 (0–.01)	.09
Mushrooms, doses	.02 (.07)	0 (0–.25)	.003 (.007)	0 (0–.02)	0 (0)	0(0–0)	.02
Tranquilizers, doses	.23 (.83)	0 (0–3)	.003 (.01)	0 (0–.04)	.4 (1.9)	0 (0–11)	.87
Opiates, doses	.25 (.86)	0 (0–3.13)	.02 (.08)	0 (0–.31)	.2 (1.2)	0 (0–8)	.71
LSD, doses	0	0	.03 (.07)	0 (0–.25)	0 (0)	0(0–0)	.0003
Ketamine	.13 (.49)	0 (0–1.75)	.001 (.005)	0 (0–.02)	0	0	.08

^aKruskal-Wallis test^bpost-hoc test Lighter group differ from None (p<.02)

Table 3
Adjusted Effects of Level of MDMA on Bayley Scales of Infant Development and Behavioral Rating Scales from 4–24 Months

	Bayley Scales of Mental Development (MDI)		Bayley Scales of Motor Development (PDI)		Attention/Arousal (at 4 months)		Orientation/engagement		Emotional regulation		Motor quality (75%)	
	Estimate (se)	p	Estimate (se)	p	b (se)	p	Estimate (se)	p	Estimate (se)	p	Estimate (se)	p
Non MDMA ^a	2.78 (1.80)	.14	6.16 (2.56)	.02	12.64 (7.60)	.10	1.24 (7.02)	.86	-1.85 (7.48)	.81	0.75 (0.40)	.06
Lighter MDMA ^a	3.26 (2.31)	.16	11.46 (3.09)	<.001	21.48 (10.00)	.03	10.83 (8.84)	.23	0.42 (9.44)	.96	0.93 (0.41)	.02
Age	0.45 (0.12)	<.001	-0.71 (0.48)	.14	-1.30 (2.34)	.58	-8.64 (2.85)	.003	-5.08 (2.83)	.08	0.08 (0.02)	<.001
Age ²			0.04 (0.02)	.01			0.23 (0.08)	.003	0.15 (0.07)	.04		
Male	5.31 (2.19)	.02	7.98 (2.77)	.005	8.79 (5.13)	.09	-14.61 (4.88)	.004	-15.31 (5.16)	.004	-0.52 (0.28)	.06
Male*Age	-0.72 (0.17)	<.001	-0.69 (0.16)	<.001								
Alcohol							3.74 (2.21)	.096				
Cocaine			-9.55 (7.21)	.19								
HOME Score	0.69 (0.18)	<.001					0.75 (0.70)	.29	1.45 (0.72)	.046	0.06 (0.03)	.053
Parity			-0.85 (0.77)	.27								

Note. Blank space indicates that the variable did not meet the criteria (e.g., not significant at the bivariate level) and therefore not included in the model; --- indicates variables not applicable.

^aThe reference group is Heavier MDMA group. Males are coded as 1, females 0.