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Motor delays in MDMA (ecstasy) exposed infants persist to 2 years

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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.

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.

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, 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, 2013; Greer and Tolbert, 1986; Sessa, 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, 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 et al., 2003), produces

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oxytocin release (Kirkpatrick et al., 2014) and reverses the action of the serotonin transporter (SERT) leading to depletion of up to 80% of available serotonin with use (Ricaurte et al., 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, 2013). Current data suggest MDMA is more likely to be used by women (Wu et al., 2009), and is often mistakenly perceived as a safe and even beneficial drug, making it a particular concern for women of reproductive age (Sessa and Nutt, 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 et al., 2014a, 2014b), have all been demonstrated to have detrimental effects on the fetus. Woman 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 et al., 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 et al., 2007).

MDMA has been demonstrated to cross the placenta in pregnant rats (Campbell et al., 2006) with correspondent levels in the fetal brain. Preclinical studies (Skelton et al., 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 et al., 2009). Neonatal exposure in rat models, for example, produced impaired path integration learning (Vorhees et al., 2004) possibly through changes in the release of dopamine and serotonin in the striatum and hippocampus (Galineau et al., 2005). MDMA treatment prenatally of pregnant rats led to reduced bodyweight and reduced learning of motor skills in adulthood (Adori 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 et al., 2010), as had been shown previously by Meyer (Meyer et al., 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 et al., 1999). Similar cardiac malformations as well as spontaneous abortions were noted in another study in the Netherlands (van Tonningen-van Driel et al., 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-Brocks Syndrome (Singer 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 et al., 2012b). At 24 months, the heavier group also had motor deficits compared to light and non-exposed children (Singer et al., 2015).

Little is known about patterns of use, and the demographics of women who use MDMA during pregnancy. Ho et al. (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 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 et al., 2010; Moore et al., 2011; Singer et al., 2012a; Singer et al., 2012b; Singer 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 et al., 2010; Moore 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 (U.K.) 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 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

et al., 2002). Women were requested to describe their intake of substances commonly used in U.K. cohorts based on prior UEL drug questionnaires (Parrott et al., 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 (g), 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 (±4) tablets in the month prior to pregnancy compared to .12 ± .2 tablets for lighter users (Wilcoxon test $p < .007$); 1.6 ± 2 vs. .12 ± 1 tablets in the first trimester ($p < .12$), and .15 ± .6 vs. .02 ± .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 ± .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 et al., 2012a).

2.4. Maternal drug use, demographics, and psychological measures

The Drug Abuse Screening Test (DAST) (Skinner, 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, 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 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, 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 and Bradley, 1984).

2.5. Infant developmental outcomes

The Bayley Scales of Infant Development III (Bayley, 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 et al., 2012a; Singer 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.

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)	
Maternal characteristics				
White, N (%)	12 (92)	10 (83)	51 (75)	.35
Registered disabled, N (%)	0	0	5 (8)	.40
Married/with partner, N (%)	10 (77)	9 (75)	57 (84)	.68
Family income, N (%)				.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
Child characteristics				
White, N (%)	10 (77)	9 (75)	51 (75)	.99
Male, N (%)	8 (62)	10 (83)	31 (46)	.04[c]
Special Baby Care Unit, N (%)	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), N (%)	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

[a] Significant post-hoc (p < .05) difference with Tukey correction between Heavier group vs. None.
[b] No significant post-hoc group difference.
[c] Significant difference between MDMA exposed group vs. None.
[d] Wechsler Abbreviated Scale of Intelligence.
[e] General Severity Index.
[f] Drug Abuse Screening Test.
[g] Home Observational Measure of the Environment.

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, birth weight, prematurity, length, or head circumference although this finding is inconclusive for birth length and head circumference due to missing data. As reported previously (Singer 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 and Michaelis, 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 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 × 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 (Fig. 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 × 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.

4.2.1. 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

Table 2
Maternal drug use during pregnancy by heavier, lighter, and non-MDMA exposure.[a]

Drug, per week	MDMA status						p
	Heavier (N = 13)		Lighter (N = 15)		None (N = 68)		
	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

[a] Kruskal–Wallis test.
[b] Post-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. Males are coded as 1, females 0.
[a] The reference group is Heavier MDMA group.

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 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 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 and Levitt, 2011). MDMA also increases cortisol levels in adult users, which may have indirect effects on fetal serotonergic activity (Parrott et al., 2014a, 2014b). 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 et al., 2012) after MDMA exposure. Adori 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 et al. (2014).

Although there are no comparable human studies of MDMA exposure, after prenatal exposure to methamphetamine, a similar amphetamine type drug, Smith 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 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 and Fornal, 1995; Wurtman, 2005).

Although the sample size of the present study is small, the homogeneity of the sample, primarily middle-class, employed, married, and

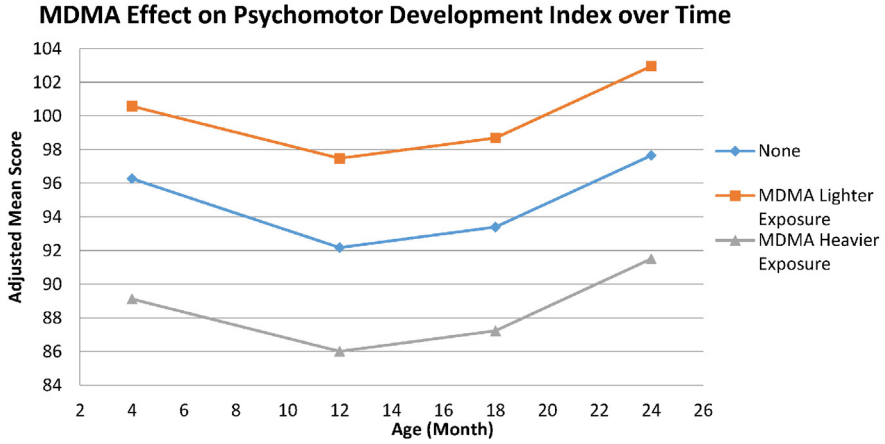

Fig. 1. Estimated means of Bayley psychomotor development index by level of MDMA exposure at each assessment age, adjusted for age^2, infant gender, interaction of infant gender and assessment age, parity, and prenatal cocaine exposure. Heavier group differs from None ($p < .05$) and from Lighter group ($p < .001$).

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 and Ferrer-Donato, 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 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, 2005; Topp et al., 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.

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Conflict of interest

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Transparency document

The Transparency document associated with this article can be found, in the online version.

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