Published in final edited form as:

Acta Paediatr. 2013 April ; 102(4): 424–430. doi:10.1111/apa.12136.

Auditory evoked arousal responses of 3-month-old infants exposed to methamphetamine *in utero*: a nap study

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Abstract

Aim—To investigate whether or not infants exposed to methamphetamine prenatally have impaired arousal responses from sleep.

Methods—The polygraphic nap studies involved 42 infants aged 3 months exposed to methamphetamine *in utero* and a comparison group of 57 infants. A proportion of mothers in both groups smoked cigarettes and/or marijuana and drank alcohol during pregnancy. White noise from 50 to 100 decibels (dB) was administered at 10 dB intervals twice within non-rapid eye movement (NREM) and rapid eye movement (REM) sleep states and arousal thresholds measured.

Results—Combining groups, 306 tests were completed (128 and 178 within REM and NREM sleep, respectively) and infants were more likely to wake at lower thresholds in REM than NREM sleep (hazard ratio 5.58; 95% CI, 3.78–8.23 $p < 0.0001$). No significant differences in arousal threshold were found between methamphetamine and comparison groups, before or after controlling for other substance use (NREM sleep; 0.98, 95% CI, 0.60–1.59 and REM sleep; 1.03, 95% CI, 0.56–1.89).

Conclusions—These findings suggest that arousal responses of methamphetamine-exposed infants remain intact, providing no support for the hypothesis that prenatal exposure could increase their vulnerability to sudden infant death syndrome (SIDS) through arousal deficits.

Keywords

EEG; heart rate; REM; SIDS; substance abuse

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SUPPORTING INFORMATION

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INTRODUCTION

Methamphetamine is a drug of abuse manufactured by chemical conversion from the decongestant pseudoephedrine, which is available on prescription in many countries. In New Zealand, a 2008 national survey reported amphetamine type stimulants as the second most widely used recreational drugs with 2.5% of those sampled using methamphetamine (1). Methamphetamine resembles cocaine but has a longer duration of action (4–24 h). It is a highly addictive stimulant, exerting its wake-promoting effects through elevating monoaminergic tone caused by blockade of the dopamine transporter and possibly other monoamine transporters. Primate experiments show that doses similar to human illicit drug use are neurotoxic to the central nervous system, and human data shows brain abnormalities in respect of inflammation, reduced neuronal density, reduced density of dopaminergic and serotonergic markers, and striatal abnormalities that may persist for years beyond cessation (reviewed in Chang et al. (2)). Short-term effects of methamphetamine include an initial rush, increased energy, a general sense of well-being, and loss of appetite, lasting 6–8 h. Adverse effects include restlessness, insomnia, hyperthermia and sometimes convulsions. Long-term use can lead to addiction, paranoia, mood disturbances, agitation, psychosis and cognitive impairment, much of which is linked to the neurotoxic effects of the drug.

No national statistics are available on current methamphetamine use during pregnancy, but past statistics report 10% of referrals to the local National Women's Hospital Alcohol Drug and Pregnancy Team in 2001 used methamphetamine, escalating to 45% in 2003 (3). Methamphetamine is linked with a number of poor clinical outcomes associated with pregnancy, birth and the neonatal period (4). Like cocaine, methamphetamine has vasoconstrictive effects, resulting in decreased uteroplacental blood flow and foetal hypoxia. Whether or not methamphetamine is neurotoxic to the developing brain of the foetus is unknown and can only easily be assessed through behavioural state profiling.

Beyond birth, the ability of an infant to arouse from sleep to a wake-promoting stimulus can be used as a marker for the functional integrity of neuronal processes (including autonomic processes) associated with arousal and cortical activation. Impaired homeostatic responses, including failure of an infant to arouse or respond to life-threatening stimuli during sleep (e.g. asphyxia through rebreathing face down on soft bedding) at a critical period in development, have been linked to sudden infant death syndrome (SIDS). Central to this hypothesis are the neuro-histological studies from SIDS victims in relation to neural networks within the medulla oblongata. These networks comprise of serotonergic (5-HT) source neurons and their projection sites that help mediate homeostatic responses during the sleep–wake cycle. Various abnormalities in multiple markers of the medullary 5-HT system in SIDS cases have been reported in three independent data sets since 2000 (5,6).

Infants exposed *in utero* to illicit drugs in general (cannabis, opiates and cocaine) are at increased risk of SIDS (7,8), as are those exposed *in utero* to tobacco (9). With the rise in methamphetamine abuse, it is important to test whether infants exposed to this drug prenatally, have impaired arousal responses, perhaps indicative of neurotoxic damage to the central nervous system that may increase their vulnerability to SIDS. To test this, we studied a subgroup of infants at 3 months of age who were recruited antenatally into an ongoing

longitudinal study of the developmental outcomes of infants exposed to methamphetamine *in utero*; the NZ-Infant Development, Environment and Lifestyle (NZ-IDEAL) study.

METHODS

Ninety-nine infants completed the sleep study. Forty-two were exposed to methamphetamine *in utero*, and 57 were not exposed (comparison group). Table 1 gives the demographic information in relation to the mother and infant. Researchers were blind to the status of participants throughout the study, including the period of data analysis. Ethical approval was obtained from the NorthernX Regional Ethics committee (NTX06/06/068). Parent/s or guardian/s gave signed consent for their infant to be involved in the study.

Recruitment

Both methamphetamine-exposed and non-exposed participants for the main study were recruited antenatally through the local maternity unit at Auckland City, North Shore and Waitakere Hospitals. Details of inclusion/exclusion criteria have been described previously (10). Mothers completed the Substance Use Inventory (11) within a few days of birth. In the present study, a status of yes/no was used to categorize substance use status. Exposure status for all illicit drugs, alcohol and tobacco were determined by self-report and meconium toxicology for drug metabolites, except for alcohol that was based on self-report as described previously (11). During their maternal and infant assessment visit at 1 month of age, participants were invited to enrol in the 3-month sleep study.

Procedures

Assessments were scheduled to coincide with the infant's normal daytime nap. All infants were studied during sleep after a breast- or bottle-feed. They were set up to record from the following polysomnography channels using the Compumedics E-series (Compumedics Ltd; Australia): two electro-encephalograms (EEG; C4/A1, C3/A2) according to the 10–20 placement system), two electro-oculograms (EOG) chin electromyogram (EMG), respiratory pattern from thoracic and abdominal respiration bands and pulse oximetry (Masimo Radical 7 monitor; Masimo Corp, Irvine, CA) and ECG (modified lead II position). Infants were put to sleep supine in a small cot. The head end of the cot held a speaker unit that emitted white noise over a range of 50–100 decibels (dB) calibrated by a sound level meter. Once sleep state was firmly established, and within no less than 5 min, the auditory stimulus was emitted beginning at 50 dB, and successively and incrementally (10 dB) emitted every 1.5 min until the baby woke fully or the maximum 100 dB intensity was reached. Stimulus duration was 3 sec. The 50–100 dB range of intensities were administered twice in non-rapid eye movement (NREM) and rapid eye movement (REM) sleep states, the order of which varied depending on the state shifts of the individual infant. If the infant switched sleep state during a test, the test was abandoned until a new sleep state was established. The duration of recordings from sleep onset to the end of the study ranged from 25 to 165 min (median 53 min). The end of the study coincided with the spontaneous end to the napping period, or the infant would not resettle after having been woken from a test.

The criteria for arousal thresholds during experimentation were based primarily on behavioural responses. The EEG data and video data were then reviewed offline to confirm arousal thresholds had been reached. A stimulus arousal occurred immediately in response to the auditory stimulus. A delay in arousal was rare and not counted as a stimulus arousal. A spontaneous arousal occurred independent of a known stimulus and was not counted if it occurred within the 30 sec after an auditory stimulation.

Polysomnographic evaluation

Sleep scoring was performed offline via the Profusion 2 software (Compumedics Pty Ltd). Sleep stages were scored as NREM (non-rapid eye movement), REM (rapid eye movement) sleep in 30-second epochs. Arousals were marked as an abrupt shift in EEG frequency according to the criteria of the Atlas Task Force (12) and meeting the later published criteria for the consensus of scoring of arousals in infants aged 1–6 months (13). The proportion of time spent in each sleep stage was expressed as a percentage of total sleep time (TST). Arousals were expressed as the total number of arousals per hour of sleep time (arousal index).

Statistical Analysis

A Kruskal–Wallis test, Poisson regression or linear regression based on log transformation of data was used to compare the demographic characteristics and polysomnographic data between methamphetamine and comparison groups. Repeatability of arousal thresholds within NREM and REM sleep states were tested using intraclass correlations. Hazard ratios were calculated using a discrete time version of the proportional hazards model, with sandwich variance estimated to adjust for repeat observations. In the current context, the hazard ratio is an expression of the hazard or chance of the infant in the test group (e.g. methamphetamine) arousing to the auditory stimulus (over the 50–100 dB protocol), as a ratio of the chance of arousal occurring in the comparison arm. p-values <0.05 were considered statistically significant.

RESULTS

Table S1 shows that methamphetamine and non-exposed comparison group infants were comparable with regard to male/female ratio, gestational age, weight, length and head circumference (at birth and study) and age at study, with more non-exposed infants exclusively breast-fed at study. The proportion of mothers educated beyond school certificate level was similar between the groups as were those supported by a benefit. The proportion of infants identified by their parent/s as Māori (indigenous New Zealanders), was significantly higher in the methamphetamine than comparison group (64% and 38%, respectively). This was higher than the regional average of 23% (14). Maternal smoking was more common in the methamphetamine group than the comparison group during pregnancy (93% vs 61%) and 1 month after birth (67% vs 46%). The prevalence of maternal alcohol consumption was similar between groups, but marijuana use was more common in the methamphetamine group during pregnancy, but not at 1 month.

Sleep, heart rate and oxygen saturation data

Summary data are given in Table 1. No significant differences were found in any of the relative sleep stages, baseline heart rate or oxygen saturation data between methamphetamine and comparison groups. It is important to point out that the sleep data for both groups represent values obtained within a fragmented sleep study protocol and are not comparable to naturalistic sleep patterns that would yield higher sleep efficiency and longer sleep duration.

Arousal thresholds

The total number of arousal tests successfully completed in the 99 infants was 128 and 178 for REM and NREM, respectively, of a possible 198 for each sleep state. Within sleep states, arousal thresholds were significantly repeatable with intraclass correlations of 0.68 and 0.60 for NREM and REM sleep, respectively. Mean $\pm$ SD arousal threshold for NREM sleep were 85 dB (IQR; 80–90), and for REM sleep, 65 dB (IQR; 60–70). Consequently, survival analyses showed infants were far more likely to wake earlier when tests were given in REM than NREM sleep (hazard ratio 5.58; 95% CI, 3.78–8.23 $p < 0.0001$). This difference was similar for both the methamphetamine (hazard ratio 6.87; 95% CI, 3.83–12.40 $p < 0.0001$) and comparison groups (hazard ratio 5.33; 95% CI, 2.98–9.54 $p < 0.0001$). Survival curves plotted according to sleep state in methamphetamine-exposed and non-exposed comparison groups are given in Figure 1. All infants woke from the test in REM sleep, 7 infants from 9 tests failed to wake to the 100 dB in NREM sleep. Hazard ratios for arousal threshold comparisons are shown in Table 2 for the following substance use during pregnancy: (i) methamphetamine vs none; (ii) tobacco vs none; (iii) marijuana vs none; and (iv) alcohol exposure vs none. Both univariate and multivariate (controlling for all other conditions) data are given. The results show no significant difference in regard to the survival data analyses for any of the group comparisons.

DISCUSSION

The data presented here do not support our hypothesis that arousal thresholds in infants exposed to methamphetamine *in utero* are compromised in comparison with infants not exposed to methamphetamine *in utero*. The findings do not explain why infants exposed to substance abuse *in utero* at increased risk of SIDS.

To the best of our knowledge, this is the first study to test arousal responses and sleep in infants exposed to methamphetamine *in utero*. The mothers in this study were polysubstance users, which is often the case, making it difficult to reach simple conclusions about the effects of one drug. However, our findings are similar to what others report. Sarfi et al. (15) found no differences in sleep–wakefulness patterns of 3-month-old infants exposed to opiates *in utero*, compared with control infants, and Hanft et al. (16), in a matched case control study of 17 infants of substance abusing mothers, reported no change in sleep state organization measured over several time points during the first year of life. Our findings support the notion proposed by these authors (16) that sleep system regulators must be highly resilient and well organized to preserve the arousal responses of infants exposed to prenatal substance abuse. These authors also include sleep architecture into that notion of

protection, but our study was too short and fragmented to study this aspect. Sleep is considered an important activity of the brain during early development facilitating brain plasticity (reorganization of neural pathways based on new experiences and information), and therefore, the concept of protection from the neurotoxic effects of methamphetamine, or other substances, is an entirely reasonable proposition. On the other hand, one very small study showed 9-week-old infants of substance abusing mothers took longer to arouse from a hypercapnic challenge during sleep compared with control infants (17).

Sleep–wake disturbances may be apparent during the period of withdrawal soon after birth. For example, sleep deprivation, disorganization and fragmentation were found in newborns experiencing neonatal abstinence syndrome and was associated with the severity of the withdrawal, with stabilization of sleep–wake regulation once the neonates were treated (18). Infants drinking breast milk containing nicotine experience alterations in sleep architecture and shortened sleep (19) with plausible biological hypotheses linking nicotine with sleep inhibition. It is possible the use of tobacco, marijuana or alcohol used prenatally could have dampened or enhanced arousal responses in both groups. Little is known about how prenatal alcohol or marijuana exposure influences later infant arousal responses. After controlling for other drug use, we did not find an effect of nicotine exposure from tobacco smoke on arousal responses of infants, confirming our previous work in relation to cortical arousal to a rebreath test where tobacco was the only substance used antenatally in 97 compared with 96 control infants (20). Infants in that study were also approximately 3 months of age and sleeping supine. Similarly, arousal responses to nasal air jet stimulation were not influenced by maternal smoking *in utero* in a similar aged infants sleeping supine (21). However, another study of 3-month-old infants reported reduced arousal responses from REM sleep to auditory stimulation during overnight sleep infants exposed to maternal smoking *in utero* (22).

Along with maternal cigarette smoking, marijuana use and alcohol consumption during pregnancy were features of both the methamphetamine and comparison group of infants. Whether or not *in utero* alcohol consumption or marijuana use per se affects arousal responses of infants at 3 months of age is unknown. In the current study, multivariate analysis, controlling for other substance use, did not reveal any arousal differences related to methamphetamine, marijuana, tobacco or alcohol use. As far as we are aware, no comparable arousal studies addressing marijuana or alcohol use exist. Results from one preliminary study conducted 24–36 h after birth showed *in utero* alcohol exposure, but not marijuana, heightened the frequency and duration of spontaneous arousals in neonates (23).

The largest study to date to examine prenatal exposure to methamphetamine and subsequent neurobehavioural patterns at one month of age reports reduced alertness, low tone, poorer quality of movement and increased stress (10). The infants who participated in the present physiological study were a subsample of the New Zealand arm of that study. Thus neurotoxic effects appear to manifest at the behavioural testing level in infants, but not at the physiological testing level of arousal from sleep. It is plausible to suggest that (i) arousal measures may not be sensitive enough to expose neurotoxic effects; (ii) sleep may be a protective state in early development in the face of adversity to facilitate brain plasticity; (iii) arousal responses during sleep are under control of the autonomic nervous system and neural

integration within the hypothalamus may be protected, whereas neural integration of higher order processes involved with neurobehavioural outcomes may not.

Our groups did not differ on heart rate measured within REM or NREM sleep states. Scheutze and Eiden (24) in a study of 4- to 8-week-old infants exposed to cocaine prenatally reported increased heart rate during sleep of exposed infants and infants exposed to higher doses of cocaine had higher heart rate variability compared with those exposed to lower amounts of cocaine or non-exposed infants. Another study found no difference at birth in regard to prenatal cocaine and infant heart rate and heart rate variability (25). Methamphetamine is a similar drug to cocaine in terms of its sympathomimetic properties, but we did not measure heart rate variability or consider the level of prenatal exposure to methamphetamine. The amount consumed and the timing of the exposure might all be important. This could be an important focus of future research as high heart rate variability in early infancy is predictive of behavioural measures of dysregulation later in infancy and into childhood (26).

Another approach to investigating the outcome of potential pre-natal neurotoxicity on the developing CNS is to assess the power characteristics of the EEG over different regions of the brain. Scher et al. (23) using this approach found that after controlling for various covariates, prenatal cocaine exposure was associated with low spectral EEG power at 1 year of age, indicating neurotoxic effects of cocaine persist well beyond the birth period. The findings also indicate that EEG power may be a useful quantitative marker, sensitive enough to detect differences between exposed and non-exposed infants. Measuring EEG power may be worth pursuing in future research as our findings are based mainly around a different experimental marker for CNS development, that is, the arousal threshold.

Our methamphetamine and comparison groups differed in respect of more infants exposed to methamphetamine prenatally were not breast-fed at 3 months, M ori ethnicity was higher and tobacco use more prevalent during pregnancy and 1 month after birth, and marijuana use was higher during pregnancy but not at 1 month. Maternal tobacco use was high in the exposed group at 98% during pregnancy, dropping to 67% one month after birth. Maternal tobacco use was also high in the comparison group, much higher than the national average, but representative of the larger study at 53%. Our groups, however, did not differ in respect of an indicator for socio-economic status and maternal education, namely receiving a benefit and education beyond 5th form, respectively. The 5th form represents the year a child has the first opportunity to leave school at age 15. Schooling in New Zealand can continue on for two more years. Three measures of growth were used in this study: weight, length and head circumference. No differences between groups were found with any of these measures.

The findings in respect of sleep state differences were expected and highlight the differences in arousal thresholds between states with REM being the lighter and more arousable state of sleep in infants (27). Previous authors have only tested auditory responses in one state, namely NREM sleep to preserve the sleep structure (28). However, preserving the sleep structure was not the intention of this protocol; rather our intention was to document an arousal threshold for each sleep state.

There were limitations to this study. Firstly, the overlap of illicit substance use in the methamphetamine group meant that we could not isolate this group to a methamphetamine only group. This would be near impossible to achieve because it is well documented that illicit drug users do not usually confine their habit to just one substance. Furthermore, maternal smoking became a confounder within both groups and was common in both groups. However, it could be argued that our non-exposed infants are a better comparison group for methamphetamine effects than if we were to use a group free of alcohol, marijuana or tobacco exposure. Secondly, the studies were conducted over a daytime nap in the laboratory setting and their sleep may not truly represent that occurring in their home environment. Their total sleep time was short, restricted by the protocol, but conditions were the same for every infant. A fourth limitation was that not all infants aroused at the maximal 100 dB threshold making it impossible to assign an exact arousal threshold in NREM sleep. Infants in this study were not tested for hearing at the time of study, but were subsequently tested at 9 months of age and all were found to have normal hearing. More breast-fed infants were represented in the comparison than methamphetamine group. Therefore, we cannot exclude this as a confounder in the arousal response as a previous study of similar aged infants report lower arousal thresholds in breast compared with bottle fed infants in REM sleep (29). Strengths of this study include the gold-standard polysomnographic recordings used to measure sleep and arousal, and the much higher number of infants included in the study (total = 99) compared with previous published studies reporting on maternal substance use and infant arousal.

In conclusion, *in utero* exposure to maternal methamphetamine use was not associated with any adverse outcomes in relation to physiological measures of arousal. Our data do not shed any light on why infants of substance abusing mothers are more at risk of SIDS than non-exposed infants. To demonstrate neurotoxicity at 3 months of age, the arousal paradigm may have lacked sensitivity and further research could be aimed at more sensitive physiological measures of neural development, for example, EEG power or heart rate variability. Neurobehavioural differences between methamphetamine-exposed infants and comparison infants have been identified one month post-partum (10). Whether these differences are linked to later developmental outcomes is yet to be established. However, finding a sensitive marker for following neural patterns from birth may help isolate the biological and/or environmental influences that could alter neurobehavioural trajectories over the long-term. If no marker exists, then the environment may play a much bigger role than previously thought.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors wish to thank the parents and caregivers of infants involved in the study. The study was funded in part by Cure Kids (Principal Investigator Edwin Mitchell with Co-Investigators Trecia Woules, Gillian Nixon and Alistair Stewart). Additional funding was provided by the National Institute of Drug Abuse: Principal Investigators were Linda LaGasse, PhD (NZ IDEAL study - R01DA21757) and Barry Lester, PhD (IDEAL study in the US - R01DA14948) and by The Auckland Medical Research Foundation (Principal Investigator Trecia Woules PhD with Co-Investigators Linda LaGasse, Barry Lester, Edwin Mitchell, Carl Kuschel). Trecia Woules is also the site

Principal Investigator of the NZ IDEAL study. We thank NZ IDEAL for permission to contact and recruit some of the subjects enrolled in their study and are grateful for the assistance their study team, particularly the Lorraine Coelho and Carolyn Ho. Andrew Morley conducted the first few sleep studies.

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Key notes

- Our nap polysomnographic study of 3-month-old infants pre-natally exposed to methamphetamine shows arousal responses (provoked by auditory stimulation) are not different to those of a comparison group not exposed to methamphetamine.
- Thus, arousal responses remain intact, and no light was shed on why infants exposed to substance abuse *in utero* are among those at high risk of SIDS.

Figure 1.

Kaplan-Meier curves showing the proportion of tests where infants were still asleep in REM and NREM sleep comparing methamphetamine (dashed lines) and control groups (solid lines).

Table 1

PSG variables within the nap study to compare group data

Variable *	Non-exposed (n = 57)	Methamphetamine-exposed (n = 42)	p-Value
Sleep Latency	8.5 (1–27.5)	5.5 (1–35.5)	0.63 [†]
Total Sleep Time	33 (27–42)	33 (29–42)	0.67
Sleep Efficiency	67 (53–82)	63 (44–87)	0.99
% NREM	69.8 (60.9–75.3)	63.9 (54.3–69.6)	0.12
% REM	29.5 (22.6–38.9)	34.9 (26.5–45.7)	0.15
% Indeterminate	0 (0–1.3)	0 (0–3.2)	0.28
Heart rate NREM	116 (109–122)	117 (113–124)	0.67
Heart rate REM	121 (116–127)	122 (119–129)	0.29
Oxygen saturation	99 (98–100)	99 (98–100)	0.54 [†]
Stimulus arousal [#]	2 (1–4)	3 (2–4)	0.11

Data are median (interquartile range).

Statistical comparisons were poisson regression or

* Variable data measured within the nap study period where auditory stimuli were repeatedly applied to evoke arousal.

[†] linear regression after log transformation.

[#] Number of auditory tests inducing an arousal

Table 2

Hazard ratios and 95% CI for arousal threshold data according to maternal substance use during pregnancy

Substance use vs none	Univariate		Multivariate*	
	NREM sleep	REM sleep	NREM sleep	REM sleep
Methamphetamine	0.90 (0.60, 1.34)	0.99 (0.63, 1.58)	0.98 (0.60, 1.59)	1.03 (0.56, 1.89)
Tobacco	1.02 (0.64, 1.62)	0.99 (0.58, 1.70)	1.24 (0.72, 2.13)	0.98 (0.54, 1.80)
Marijuana	0.78 (0.52, 1.18)	0.97 (0.61, 1.55)	0.75 (0.45, 1.23)	0.95 (0.53, 1.72)
Alcohol	0.89 (0.59, 1.33)	1.04 (0.66, 1.66)	0.89 (0.58, 1.37)	1.05 (0.65, 1.69)

* Adjusted for the other substances.