Mid-gestational enlargement of fetal thalami in women exposed to methadone during pregnancy

Meredith Schulsün,1 Anthony Liu,2,3 Tracey Björkman,1 Ann Quinton,1,4 Kristy P. Mann,4 Ron Benzie,4 Michael Peek,2,4 and Ralph Nanan1,2*

1 Discipline of Paediatrics, Sydney Medical School – Nepean, The University of Sydney, Penrith, NSW, Australia
2 Charles Perkins Centre – Nepean, The University of Sydney, Penrith, NSW, Australia
3 Perinatal Research Centre, UQ Centre for Clinical Research, The University of Queensland, Herston, QLD, Australia
4 Discipline of Obstetrics and Gynaecology, Sydney Medical School – Nepean, The University of Sydney, Penrith, NSW, Australia
5 NHMRC Clinical Trials Centre, The University of Sydney, Camperdown, NSW, Australia

Methadone maintenance therapy is the standard of care in many countries for opioid-dependent women who become pregnant. Despite recent evidence showing significant neurodevelopmental changes in children and adults exposed to both licit and illicit substances in utero, data on the effects of opioids in particular remains scarce. The purpose of this study was to examine the effects of opiate use, in particular methadone, on various fetal cortical and biometric growth parameters in utero using ultrasound measurements done at 18–22 weeks gestation. Head circumference (HC), bi-parietal diameter, lateral ventricle diameter, trans cerebellar diameter, thalamic diameter, cisterna magna diameter, and femur length were compared between fetuses born to methadone-maintained mothers and non-substance using controls. A significantly larger thalamic diameter (0.05 cm, \( p = 0.01 \)) was observed in the opiate-exposed group. Thalamic diameter/HC ratio was also significantly raised (0.03 mm, \( p = 0.01 \)). We hypothesize here that the increase in thalamic diameter in opiate-exposed fetuses could potentially be explained by regional differences in opioid and serotonin receptor densities, an alteration in monoamine neurotransmitter systems, and an enhancement of the normal growth increase that occurs in the thalamus during mid-gestation.

Keywords: pre-natal drug exposure, methadone, opiates, neurodevelopment, neuroimaging

INTRODUCTION
Methadone maintenance therapy is the standard of care in many countries for opioid-dependent women who become pregnant (1, 2). Although there are many benefits to the use of methadone during pregnancy, it readily crosses the placenta, enters the bloodstream of the fetus and imposes potential risks (3, 4). The main documented adverse outcome of methadone use during pregnancy is the development of neonatal abstinence syndrome (NAS), with withdrawal being reported in more than 50% of infants born to methadone-maintained mothers (5). Opiate-exposed neonates have also been reported to be born prematurely and have lower birth weights, lengths, and head circumferences (HC) up to 5 years of age (6–8). Recent evidence shows that exposure to both licit and illicit substances causes significant structural brain changes in children, adolescents, and adults, which leads to the hypothesis that there may be significant effects on the brains of fetuses as well (9–11). These changes are diverse not only in terms of regions of the brain affected, but also in terms of the specific effects themselves, and occur on a cellular, macroscopic structural, and functional/behavioral level (9–13).

The size of a multitude of cortical and sub-cortical structures, the integrity of white matter tracts, changes in blood-flow pattern, and alterations in neurotransmitter levels have all been shown to be affected by different substances (9, 11, 12, 14). However, the data on the specific effects of opiates (methadone in particular) is scarce and only a few studies on their effects on brain development in humans can be identified (11, 15). One such study showed a reduction in the volumes of structures including the cerebral cortex, amygdala, and basal ganglia in children exposed primarily to heroin in utero (11). In an older study conducted with ultrasound, the thalamic cross-sectional area and HC were found to be larger in methadone-exposed infants at 6 months of age when compared to controls (15). Interestingly, in the rat opioids appear to selectively accumulate in the nervous tissues of fetal and pre-weaning rats, perhaps due to an increased permeability of their blood–brain barriers (16–18). Furthermore, research has shown that the limbic system, thalamus, and striatum appear to have among the highest concentration of opioid receptors (18), and therefore, it would seem likely that in utero opioid exposure would have the most significant effect in those areas. The studies mentioned above (11, 13) show some support for this notion, however, further evidence is needed. No evidence can be found specifically on the effect of opioid exposure in the human brain prenatally. Therefore, the purpose of this study was to examine the effects of opiate use, in particular methadone, on various fetal cortical and biometric growth parameters in utero using ultrasound measurements done at 18–22 weeks gestation. Use of such non-invasive and readily available measures could potentially allow for...
Materials and Methods

Subjects
A retrospective medical record review was conducted on fetuses born to methadone-maintained pregnant women at a tertiary birthing unit between 2000 and 2006 inclusive. Women who had undergone their fetal anomaly scans (FAS) between gestational ages 18 and 22 weeks were included in our cohort. One hundred and eight control subjects who did not use illicit drugs or alcohol were identified from the local obstetric database and matched to our subjects based on maternal age, gender of the fetus, gestational age at FAS ± 5 days, and birth month ± 2 months. Exclusion criteria for both our subjects and controls included women with preeclampsia, hypertension, diabetes mellitus, multiple pregnancies, fetuses with congenital malformations, or non-satisfactory scans (that is unable to identify or measure required parameters). This study was approved by the Human Research Ethics Committees of both the Nepean Blue Mountains Local Health District and the University of Sydney.

Parameters Measured
Images were captured on the ultrasound machines GE Voluson 730 (GE Medical Systems, Piscataway, NJ, USA), GE Voluson i (GE Medical Systems, Piscataway, NJ, USA), or Medison Accuvix V20 Prestige (Samsung Medison, Seoul, South Korea). The measurements used for our data were taken by accredited perinatal sonographers. These included bi-parietal diameter (BPD), HC, femur length (FL), transcerebellar diameter (TCD), and lateral ventricle diameter. Additionally, thalamic diameter and cisterna magna diameter were measured using Adobe Photoshop v.7.0 (Adobe Systems Inc., USA). Gestational age of the fetus was based on last menstrual period (LMP) and confirmed by an ultrasound performed before 20 weeks gestation.

Statistical Analysis
Statistical analysis was performed using SPSS v.21.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics are reported as means and standard deviations. The data was confirmed to be normally distributed and variables were compared between the opiate-dependent group and the control group using independent samples t-tests. Adjusted analysis was undertaken using multiple regression modeling. A two tailed p-value of <0.05 was considered statistically significant.

Results
Forty-two fetuses with FAS between 18 and 22 weeks were identified from our cohort of methadone-maintained mothers. The exact amount of opiate and other illicit drug use during pregnancy is intrinsically difficult to identify and is mainly dependent on self-reporting. However, our subjects were primarily opiate-dependent and ultimately maintained on methadone substitution therapy during their pregnancy. Although alcohol use was not considered an exclusion criterion, only 1 of 42 subjects reported using alcohol. Further details of this cohort are described in previous publications (19, 20) and other pertinent maternal and neonatal demographic characteristics are shown in Table 1.

### Table 1 | Maternal and neonatal characteristics.

|                          | Opiate-exposed group, n = 42 | Control group, n = 108 |
|--------------------------|-----------------------------|------------------------|
| Maternal characteristics  |                             |                        |
| Age (years)              | 27.4 ± 4.3                  | 27.4 ± 4.3             |
| Smokers                  | 39 (93%)                    | 15 (14%)               |
| Alcohol use              | 1 (2%)                      | 0 (0%)                 |
| Neonatal characteristics |                             |                        |
| Gender                   | 20 female (48%), 22 male (52%) | 53 female (49%), 55 male (51%) |
| Gestational age at FAS   | 19 ± 3 ± 5 days             | 19 ± 3 ± 5 days        |
| NAS treated with morphine| 36 (86%)                    | 0 (0%)                 |
| Urine drug screen at birth| 37 (88%)                    | 0 (0%)                 |
| Substances reported in UDS|                            |                        |
| Methadone                | 35 (94%)                    |                        |
| Opiates                  | 6 (16%)                     |                        |
| Benzodiazepines          | 4 (11%)                     |                        |
| Cannabis                 | 10 (27%)                    |                        |
| Amphetamines             | 1 (3%)                      |                        |

NAS, neonatal abstinence syndrome; UDS, urinary drug screen; FAS, fetal anomaly scan.

All parameters measured during the FAS were compared between the opiate – exposed group and the control group (Table 2). Of these, there were no statistically significant differences observed between the groups except for thalamic diameter. The diameter of the thalamus was, on average, 0.05 cm larger in the opiate-exposed group compared to the control group (p = 0.01). Adjusted for gestational age, the thalamic diameter was still significantly larger by 0.05 cm (95% CI: 0.10–0.85, p = 0.01) in the exposure group. The ratio of thalamic diameter/HC was also compared between the two groups and found to be significantly larger in the opiate-exposed group (0.90 ± 0.1 versus 0.87 ± 0.1 mm; p = 0.01). Finally, because of the known effect that cigarette smoking has on growth in the developing fetus (9, 19), comparisons of all parameters measured during the FAS between smokers and non-smokers were also performed (Table 3).

There was no statistically significant difference in any of the variables except thalamic diameter. The thalamus was, on average, 0.04 cm larger in the smoking group compared to the non-smoking group (p = 0.02). When comparing the thalamic diameter/HC ratio in the smokers versus non-smokers, the ratio was found to be significantly larger in the smoking group (0.90 ± 0.07 mm in smokers versus 0.86 ± 0.07 mm in non-smokers; p = 0.01). Smoking could not be controlled for in our patient and control group selection. As such, smoking was almost completely confounded by methadone use and it was not possible to model an interaction in this patient population. Table 4 provides a descriptive analysis, however, showing a trend toward a larger thalamic diameter with exposure to either cigarette smoking or opiate-exposure independently, with a possible cumulative effect of exposure to both.
Table 2 | Comparison of FAS measurements between opiate–exposed fetuses and controls.

| Variable                        | Controls, n = 108 (cm ± SD) | Opiate-exposed, n = 42 (cm ± SD) | Difference (control-methadone) and 95% CI | p-Value |
|---------------------------------|-----------------------------|----------------------------------|------------------------------------------|---------|
| Bi-parietal diameter            | 4.44 (0.26)                 | 4.43 (0.27)                      | 0.01 (−0.88 to 0.11)                     | 0.78    |
| Head circumference              | 16.54 (0.96)                | 16.55 (1.04)                     | −0.01 (−0.36 to 0.34)                    | 0.94    |
| Lateral ventricle diameter      | 0.77 (0.13)                 | 0.74 (0.09)                      | 0.03 (−0.01 to 0.07)                     | 0.19    |
| Cerebellar diameter             | 1.9 (0.15)                  | 1.92 (0.12)                      | −0.02 (−0.72 to 0.03)                    | 0.46    |
| Thalamus diameter               | 1.43 (0.10)                 | 1.48 (0.10)                      | −0.05 (−0.39 to −0.01)                   | 0.01    |
| Cisterna magna diameter         | 0.40 (0.08)                 | 0.42 (0.08)                      | −0.02 (−0.04 to 0.01)                    | 0.32    |
| Femur length                    | 3.02 (0.24)                 | 3.01 (0.28)                      | 0 (−0.08 to 0.10)                       | 0.85    |

Bold font indicates significant difference.

Table 3 | Comparison of FAS measurements between smokers and non-smokers.

| Variable                        | Non-smokers, n = 96 (cm ± SD) | Smokers, n = 54 (cm ± SD) | Difference (non-smokers – smokers) and 95% CI | p-Value |
|---------------------------------|-------------------------------|---------------------------|-----------------------------------------------|---------|
| Bi-parietal diameter            | 4.45 (0.26)                  | 4.43 (0.28)               | 0.02 (−0.07 to 0.11)                           | 0.65    |
| Head circumference              | 16.55 (0.92)                 | 16.52 (1.08)              | 0.04 (−0.29 to 0.36)                          | 0.83    |
| Lateral ventricle diameter      | 0.76 (0.07)                  | 0.76 (0.18)               | 0.00 (−0.04 to 0.04)                          | 0.90    |
| Cerebellar diameter             | 1.92 (0.11)                  | 1.90 (0.19)               | 0.02 (−0.03 to 0.06)                          | 0.49    |
| Thalamus diameter               | 1.43 (0.10)                  | 1.48 (0.10)               | −0.04 (−0.08 to −0.01)                        | 0.02    |
| Cisterna magna diameter         | 0.40 (0.08)                  | 0.41 (0.08)               | −0.01 (−0.04 to 0.02)                         | 0.53    |
| Femur length                    | 3.02 (0.23)                  | 3.02 (0.29)               | 0 (−0.09 to 0.08)                            | 0.89    |

Bold font indicates significant difference.

Table 4 | Descriptive analysis of thalamic diameter in four exposure groups: non-smoking controls, non-smoking opiate-exposed, smoking controls, and smoking opiate-exposed.

| Group                           | Thalamus size (cm) Mean ± SD | 95% CI               |
|---------------------------------|------------------------------|----------------------|
| Non-smoking controls (n = 93)   | 1.43 ± 0.01                  | 1.41–1.45            |
| Non-smoking opiate-exposed (n = 3) | 1.46 ± 0.05                | 1.35–1.56            |
| Smoking controls (n = 15)       | 1.45 ± 0.03                  | 1.39–1.50            |
| Smoking opiate-exposed (n = 39) | 1.48 ± 0.17                  | 1.45–1.52            |

DISCUSSION

An analysis of several parameters measured during the FAS of opiate-exposed and control fetuses has demonstrated a significant increase in the thalamic diameter in opiate-exposed fetuses. The thalamic diameter/HC ratio was also significantly increased in the opiate-exposed group, indicating that the thalamus grew out of proportion with the rest of the head. This result was unexpected, and is difficult to explain due to limited literature on the topic. Only one previous study has looked specifically at thalamic size and is difficult to explain due to limited literature on the topic. This study used ultrasound to demonstrate that thalamic area was not and an older histochemical study (24), however, have demonstrated that growth of the thalamus does not progress linearly overall, with the density of those receptors increasing with gestational age and into adulthood (18, 25). Furthermore, the thalamus is reported to have one of the highest concentrations of serotonin transporters in the brain (26), and methadone exposure has been shown to increase the concentration of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) particularly in the striatum, an area of the brain intimately connected to the thalamus (27). This is interesting, as many of the proposed neurodevelopmental effects of other substances such as methamphetamine, cocaine, and tobacco are attributed to alterations in monoamine neurotransmitter systems and these neurotransmitters reportedly play a key role in the development of the thalamus after methadone exposure.

Overall, very little is known about the normal pre-natal development of the thalamus. Both a recent 3D ultrasound report (23) and an older histochemical study (24), however, have demonstrated that growth of the thalamus does not progress linearly in humans, and that there is a striking increase in size from 20 to 28 weeks gestation, with slower growth both before and after that time. Interestingly, the thalamus has also been shown to have one of the highest concentrations of opioid receptors in the brain overall, with the density of those receptors increasing with gestational age and into adulthood (18, 25). Furthermore, the thalamus is reported to have one of the highest concentrations of serotonin transporters in the brain (26), and methadone exposure has been shown to increase the concentration of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) particularly in the striatum, an area of the brain intimately connected to the thalamus (27). This is interesting, as many of the proposed neurodevelopmental effects of other substances such as methamphetamine, cocaine, and tobacco are attributed to alterations in monoamine neurotransmitter systems and these neurotransmitters reportedly play a key role in the development of the thalamus after methadone exposure.
trophic role in brain development, particularly in the development of the thalamus (9, 28, 29). Therefore, our proposed hypothesis is that prenatal opiate-exposure alters monoamine neurotransmitter systems and somehow “ramps-up” the normal developmental increase in thalamus size that occurs around mid-gestation; the thalamus being particularly susceptible due to the increased density of both opioid and serotonin receptors. The actual functional implications of such a change in thalamic size are unknown. However, as the thalamus is responsible for an array of critical functions such as relaying information between cortical areas and transmitting peripheral stimuli to the cortex (25), the changes we have demonstrated may well prove to be clinically significant.

Briefly, although it is difficult in this case to disentangle the effects of opiates versus cigarette smoking on the size of the thalami in our subjects, it appears that nicotine may be independently causing an increase in thalamus size as well. If this is the case, it could potentially be due to nicotine’s ability to bind nicotinic acetylcholine receptors (nAChRs) and the fact that acetylcholine (ACH) plays a vital role in brain development and maturation. By binding nAChRs, nicotine has the ability to disrupt brain development and potentially alter the size of distinct brain regions (30, 31). Furthermore, nicotine, like methadone, alters monoamine systems and also has the potential to affect thalamic size in this manner (32). More research needs to be done however, specifically examining the effects of cigarette smoking on neurodevelopment.

Limitations of this research include the lack of post-natal follow-up measurements as well as the inability to independently analyze the effects of opiates and nicotine on thalamic diameter. This study would best be performed longitudinally in the future, with smoking status incorporated as a controlled parameter, tracking changes in the thalamus diameter at birth and into childhood. Also, as previously stated, determining the exact amount of opiate and other illicit drug use during pregnancy in this cohort is intrinsically difficult to identify. Therefore, confounding factors such as the effect of other substances potentially used during pregnancy must be considered.

CONCLUSION

Opiate-exposure (primarily methadone) is associated with a significant increase in thalamic diameter when compared to controls. This could potentially be attributed to regional differences in opioid and serotonin receptor densities, an alteration in monoamine neurotransmitter systems, and an enhancement of the normal growth increase that occurs in the thalamus during mid-gestation. Pre-natal nicotine exposure also appears to increase the size of the thalamus, though the effects are difficult to separate from that of the opiates. None of the other growth parameters measured during the FAS between 18 and 22 weeks were significantly different to controls.

ACKNOWLEDGMENTS

We express our gratitude to Mr. Brendan Mein for assistance in gathering of data.

REFERENCES

1. Dunlop C, Panjari M, O’Sullivan H, Henschke P, Love V, Ritter A, et al. Clinical Guidelines for the Use of Buprenorphine in Pregnancy. In: Victoria DHS, editor. Fitzroy: Turning Point Alcohol and Drug Centre (2003). p. 1–49.
2. Wong S, Ordean A, Kahan M. Maternal fetal medicine committee, family physicians advisory committee, medico-legal committee, society of obstetricians and gynaecologists of Canada. Substance use in pregnancy. J Obstet Gynaecol Can (2011) 33:367–84.
3. Burns L, Mattick RP, Lim K, Wallace C. Methadone in pregnancy: treatment retention and neonatal outcomes. Addiction (2007) 102:264–70. doi:10.1111/j.1567-8547.2006.00165.x
4. Nekhayeva IA, Nanovskaya TN, Deshmukh SV, Zarikova OL, Hanks GDV, Aleksandrov MS. Bidirectional transfer of methadone across the human placenta. Biochem Pharmacol (2005) 69:187–97. doi:10.1016/j.bcp.2004.09.008
5. Jones HE, Finnegar LP, Kaltenthal B. Methadone and buprenorphine for the management of opioid dependence in pregnancy. Drugs (2012) 72:747–57. doi:10.2165/11632820-000000000-00000
6. Brown HL, Britton KA, Malaffey D, Brizendine E, Hett AK, Turnquest MA. Methadone maintenance in pregnancy: a reappraisal. Am J Obstet Gynecol (1998) 179:459–63. doi:10.1016/S0002-9378(98)07039-5
7. Kannendy SR, Albin S, Lowinson J, Berle B, Eidelman AI, Gartner LM. Differential effects of maternal heroin and methadone use on birth weight. Pediatrics (1976) 58:681–5.
8. Van Baar A, de Graaff BM. Cognitive development at preschool-age of infants of drug-dependent mothers. Dev Med Child Neurol (1994) 36:1063–75. doi:10.1111/j.1469-8749.1994.tb1809.x
9. Derauf C, Kekatpure M, Nezyi N, Lester B, Kosofsky B. Neuroimaging of children following prenatal drug exposure. Sem Cell Dev Biol (2009) 20:441–54. doi:10.1016/j.semcdb.2009.03.001
10. Rossotf P, Soderberg L, Sowell E. Structural, metabolic, and functional brain abnormalities as a result of prenatal exposure to drugs of abuse: evidence from neuroimaging. Neuropsychol Rev (2010) 20:376–97. doi:10.1007/s11065-010-9150-x
11. Walhovd KB, Moe V, Slikking K, Due-Tønnessen P, Bjørnerud A, Dale AM, et al. Volumetric cerebral characteristics of children exposed to opiates and other substances in utero. Neuroimage (2007) 36:1331–44. doi:10.1016/j.neuroimage.2007.03.070
12. Rao H, Wang J, Giannetta J, Korczykowski M, Shera D, Avants B, et al. Altered resting cerebral blood flow in adolescents with in utero cocaine exposure revealed by perfusion functional MRI. Pediatrics (2007) 120:1245–54. doi:10.1542/peds.2006-2596
13. Yanai J, Huleihei R, Israel M, Metsuyamn S, Shahak H, Vatoury O, et al. Functional changes after prenatal opiate exposure related to opiate receptors’ regulated alterations in cholinergic innervation. Int J Neuropsychopharmacol (2003) 6:253–65. doi:10.1017/S1461415703003523
14. Lebel C, Rasmussen C, Wyper K, Walker L, Andrew G, Yager J, et al. Brain dysfunction from within drug abnormalities in children with fetal alcohol spectrum disorder. Alcohol Clin Exp Res (2008) 32:1732–40. doi:10.1111/j.1530-0277.2008.00750.x
15. Pasto ME, Deiting J, Grauzini LJ, Ehrlich S, Finnegar LP. Disparity in hemispheric and thalamic growth in infants undergoing abstinence. NIDA Res Monogr (1986) 67:342–8.
16. Peters MA, Turnbrow M, Buchenauer D. The distribution of methadone in the nonpregnant, pregnant, and fetal rat after acute methadone treatment. J Pharmacol Exp Ther (1972) 181:273–8.
17. Shah NS, Donald AG. Pharmacological effects and metabolic fate of levomethadone during postnatal development in rat. J Pharmacol Exp Ther (1979) 208:491–7.
18. Vathy I. Prenatal opiate exposure: long term CNS consequences in the stress system of the offspring. Psychoneuroendocrinology (2002) 27:273–83. doi:10.1016/S0306-4530(01)00049-X
19. Delsing C, Van Den Wittendoer E, Liu AIW, Perek MJ, Quinton A, Mongelli M, et al. The relationship between maternal opiate use, amphetamine use, and smoking on fetal growth. Aust N Z J Obstet Gynaecol (2011) 51:446–51. doi:10.1111/j.1479-828X.2011.01342.x
20. Liu AIW, Jones MP, Murray H, Cook C, Naran N. Perinatal risk factors for the neonatal abstinence syndrome in infants born to women on methadone maintenance therapy. Aust N Z J Obstet Gynaecol (2010) 50:253–8. doi:10.1111/j.1479-828X.2010.01668.x
21. Mattson SN, Riley EP, Sowell ER, Jernigan TL, Sobel DF, Jones KL. A decrease in the size of the basal ganglia in children with fetal alcohol spectrum. Alcohol Clin Exp Res (1996) 20:1088–93. doi:10.1111/j.1530-0277.1996.tb01951.x
22. Sowell ER, Leow AD, Bookheimer SY, Smith LM, O’Connor MJ, Kan E, et al. Differentiating prenatal exposure to methamphetamine and alcohol versus alcohol
and not methamphetamine using tensor-based brain morphometry and discriminant analysis. J Neurosci (2010) 30:3876–85. doi:10.1523/JNEUROSCI.4967-09.2010

23. Sotiriadis A, Dimitrakopoulos I, Eleftheriade M, Agorastos T, Makrydimas G. Thalamic volume measurement in normal fetuses using three-dimensional sonography. Journal of Clinical Ultrasound (2012) 40:207–13. doi:10.1002/jcu.21888

24. Kostovic I, Goldman-Rakic PS. Transient cholinesterase staining in the mediodorsal nucleus of the thalamus and its connections in the developing human and monkey brain. J Comp Neurol (1983) 219:431–47. doi:10.1002/cne.902190405

25. Villiger JW, Taylor KM, Gluckman PD. Ontogenesis of opiate receptors in regions of the ovine brain. Pediatr Pharmacol (1982) 2:349–56.

26. Frankle WG, Huang Y, Hwang DR. Comparative evaluation of serotonin transporter radioligands 11C-DASB and 11C-McN 5652 in healthy humans. J Nuclear Med (2004) 45:682–94.

27. Robinson SE, Maher JR, Wallace MJ, Kunko PM. Perinatal methadone exposure affects dopamine, norepinephrine, and serotonin in the weanling rat. Neurotoxicol Teratol (1997) 19:295–303. doi:10.1016/S0892-0362(97)00018-4

28. Esaki T, Cook M, Shimozji K, Murphy DL, Sokoloff L, Holmes A. Developmental disruption of serotonin transporter function impairs cerebral responses to whisker stimulation in mice. Proc Natl Acad Sci U S A (2005) 102:5582–7. doi:10.1073/pnas.0501509102

29. Monckton JE, McCormick DA. Neuromodulatory role of serotonin in the ferret thalamus. J Neurophysiol (2002) 87:2124–36. doi:10.1152/jn.00650.2001

30. Slotkin TA. Cholinergic systems in brain development and disruption by neurotoxicants: nicotine, environmental tobacco smoke, organophosphates. Toxicol Appl Pharmacol (2004) 198:132–51. doi:10.1016/j.taap.2003.06.001

31. Slotkin TA, Seidler FJ, Qiao D, Aldridge JE, Tate CA, Cousins MM, et al. Effects of prenatal nicotine exposure on primate brain development and attempted amelioration with supplemental choline or vitamin C: neurotransmitter receptors, cell signaling and cell development biomarkers in fetal brain regions of rhesus monkeys. Neuropsychopharmacology (2005) 30:129–44. doi:10.1038/sj.npp.1300544

32. Muneoka K, Ogawa T, Kamei K, Muraoa S, Tomiyoshi R, Mumura Y, et al. Prenatal nicotine exposure affects the development of the central serotoninergic system as well as the dopaminergic system in rat offspring: involvement of route of drug administration. Brain Res Dev Brain Res (1997) 102:117–26. doi:10.1016/S0165-3806(97)00092-8

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 14 June 2014; accepted: 08 July 2014; published online: 21 July 2014.
Citation: Schulson M, Liu A, Björkman T, Quinton A, Mann KP, Benzie R, Peek M and Nanan R (2014) Mid-gestational enlargement of fetal thalami in women exposed to methadone during pregnancy. Front. Surg. 1:28. doi: 10.3389/fsurg.2014.00028
This article was submitted to Gynecology and Obstetrics, a section of the journal Frontiers in Surgery.
Copyright © 2014 Schulson, Liu, Björkman, Quinton, Mann, Benzie, Peek and Nanan. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.