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Neuroimaging in Infants with Prenatal Opioid Exposure: Current Evidence, Recent Developments and Targets for Future Research

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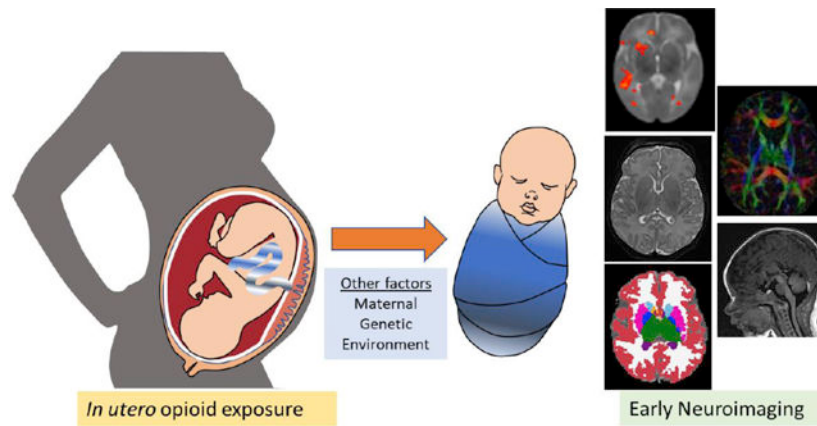
Abstract

Prenatal opioid exposure (POE) has shown to be a risk factor for adverse long-term cognitive and behavioral outcomes in offspring. However, the neural mechanisms of these outcomes remain poorly understood. While preclinical and human studies suggest that these outcomes may be due to opioid-mediated changes in the fetal and early postnatal brain, other maternal, social, and environmental factors are also shown to play a role. Recent neuroimaging studies reveal brain alterations in children with POE. Early neuroimaging and novel methodology could provide an *in vivo* mechanistic understanding of opioid mediated alterations in developing brain. However, this is an area of ongoing research. In this review we explore recent imaging developments in POE, with emphasis on the neonatal and infant brain, and highlight some of the challenges of imaging the developing brain in this population. We also highlight evidence from animal models and imaging in older children and youth to understand areas where future research may be targeted in infants with POE.

Graphical Abstract

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Keywords

Neonatal abstinence syndrome; Neurodevelopment; Addiction; Opioid use disorder

Introduction

Opioid use disorder (OUD) during pregnancy is a major public health crisis in several developed countries, with a recent sharp rise in the number of pregnant women using opioids, and a corresponding increase in the number of babies born with symptoms of opioid withdrawal, also referred to as neonatal abstinence syndrome [1, 2]. These opioid withdrawal symptoms in the neonate necessitates prolonged hospital stay and possible opioid pharmacotherapy to control symptoms [3] and these infants are also at risk of poor cognitive and neurodevelopmental outcomes[4]. The risk of poor cognitive and neurodevelopmental outcomes in prenatal opioid exposed children is multifactorial. Although actual opioid mediated alterations in brain development may play a role, other important factors include maternal and infant opioid related genetics [5–9] poly-drug, smoking and alcohol exposure, maternal and childhood malnutrition, maternal childhood stress and adverse childhood events, maternal education level and socioeconomic status [10–12]. While detailed discussion of these other factors is beyond the scope of this review, we encourage the reader to understand that the presented evidence of opioid related brain developmental alterations on imaging, and supportive evidence from animal studies should be viewed in the greater context of other mother and child genetic, socio-economic and environmental factors [11, 12].

Maternal opioids cross the placenta [13] and can influence the development, maturation and apoptosis of oligodendrocytes and neurons in the fetal brain in animal studies[14–16]. Opioids primarily exert influence through the mu, delta, and kappa opioid receptors and are critical in the regulation of several higher-level functions, including mood, reward processing, and motivated behavior [17–19]. Differential and variable expression of the opioid receptors in the mature adult brain compared to the rapidly developing brain in fetuses and infants may partly account for a differential impact of opioids on the developing brain, and could play a role in their long-term behavioral and developmental consequences[20].

Animal research in controlled settings show significant differences in behavioral phenotypes and brain molecular pathways in prenatal opioid exposure (POE) [21] in the absence of extraneous variables. However, the translatability of the findings to human fetus and neonate is complicated because of differences in neurodevelopmental trajectories, receptor expression, and central opioid pharmacokinetics. Although animal models should be interpreted with caution, these models offer valuable mechanistic insight into POE related radiologic alterations observed in humans, especially when confounding factors cannot be controlled for in human studies.

There is only limited literature on structural and functional alteration to the developing human and infant brain with POE [22–30] (Table 1) with many more neuroimaging studies in older children and youth with prenatal opioid and polysubstance exposure [31–41]. One of the major drawbacks of imaging older children and youth is that the influence of postnatal environment, including living with biological parents, socioeconomic status, parental stress, childhood nutrition, childhood adverse life events cannot be completely adjusted for. Therefore, imaging in early infancy may help without these postnatal confounding factors, although are still challenged by the prenatal and in utero environment. For example, the impact of prenatal exposures of other drug exposures on infant brain developmental alterations have been well described [39, 42–44]. Unlike alcohol, which exhibits dose-related fetal teratogenicity, brain alterations associated with opioids may be subtle, such as decreased regional brain volumes and alterations of white matter microstructure [22–26, 31]. Therefore, advanced imaging modalities are needed to recognize and quantify the impacts of POE on early brain structural and functional alterations. Based on evidence from imaging studies in infants and older children with prenatal opioid or other drug exposures, opioid-using adults, and mechanistic animal models, we discuss advanced MR imaging techniques that may be useful in studying prenatal opioid-related neural-injury and specific brain regions that would serve as potential targets for future research in infants with POE.

Imaging methods

As opioids have the potential to impact prenatal neurogenesis and oligodendrocyte-mediated white matter myelination [45, 46], fetal or early postnatal neuroimaging offer value in assessing opioid-mediated developmental alterations. However, imaging of non-sedated infants is more challenging compared to older children and adults. Imaging of infants is generally performed during sleep, which can be difficult to maintain in a loud scan environment. The unmyelinated infant brain lacks the typical contrast of the fully myelinated adult brain and can hinder accurate assessment of gray and white matter volumes. The lack of easily accessible infant brain templates, atlases, and processing pipelines also makes quantitative infant brain image analysis more resource intensive. However, recent improvements in MRI techniques, faster image acquisition with greater spatial and temporal resolution, prospective and retrospective techniques for quality control, and in particular methods to decrease motion-related artifact, allow for the increasing use of this modality to study infant brain development[47, 48].

Structural and Morphometric: Since global and regional infant brain volumes may be altered in prenatal drug exposure [23, 24], high-resolution anatomic MR sequences are

essential in morphometric neuroimaging studies. These anatomic scans can be useful to assess for the presence of brain structural injury by visual assessment [25], and also for quantitative assessment of gray and white matter volumes, myelination, gyrification, and cortical thickness. Recent tools for automated brain segmentation of the neonatal and infant brain are incredibly helpful in rapid volumetric assessment of total and regional brain gray and white matter volumes, cortical thickness, and cortical surface areas and cortical infolding using primarily T1 weighted images (Figure 1) [49, 50] or a combination of T1 weighted, T2 weighted and diffusion images [51]. Our experience has been that in spite of these automated tools, manual corrections and editing are still required because of the complex nature of the infant brain maturational contrast.

Diffusion tensor imaging (DTI), an MRI method of quantifying anisotropic water diffusion reflects white matter structural integrity. With progressive myelination and maturation of white matter tracts in the developing brain, there is an increase in fractional anisotropy (FA), and decrease in axial diffusivity (AD) and radial diffusivity (RD). The maturing white matter tracts connecting different regions of the brain form the basis of the structural connectome that is identified as early as the late second to third trimester of human fetal life [52, 53]. Identification of white matter tracts in the infant brain can be challenging, because of the relatively high brain water content and low FA, and susceptibility to motion and other artifacts. Recent advances in automated infant brain diffusion image processing are incredibly helpful in the assessment of white matter bundles [54]. Disruptions of the structural connectome are present in prematurity, hypoxic ischemic injury, and prenatal drug exposure, are shown to be predictive of early childhood neurodevelopmental outcomes [52, 55, 56].

Functional MRI (fMRI), which captures the fluctuations in blood oxygen level-dependent (BOLD) signal—a measure of neuronal activity [57, 58], is helpful in assessing functional brain network connections. Spontaneous BOLD signal fluctuations identified when the brain is at rest or during sleep (resting state fMRI, rs-fMRI) form the basis of resting state networks (RSNs). RSNs are well characterized in the adult brain and identified in the developing human brain as early as the third trimester. These RSNs continue to mature and organize after birth [59–62]. Multiple methods of analysis of rs-fMRI data exist, including the commonly described independent component analysis, seed-based analysis, and graph theory network analysis. Graph theory network analysis methods are especially useful in characterization of brain network connections, and show maturation of brain networks from more local connections in the young infant to long-range and interhemispheric network connections in childhood [63, 64]. As RSNs correlate with developmental maturation [60, 61], rs-fMRI changes could be useful in the prediction of neurodevelopmental outcome following premature birth, prenatal drug exposure, or perinatal hypoxic insult [39, 65–67].

Areas for further research in prenatal opioid exposure

Mechanistically, animal models show that drugs influence the brain through the mesocorticolimbic reward pathway, initiating in the ventral tegmental area and projecting to several subcortical and cortical regions including the amygdala, striatum, thalamus, insula and prefrontal regions [68]. In human infants, other mechanisms may also play a role in

determining opioid related brain development such as associated nutritional deficits, hypoxia, synergistic effects of other drugs, and opioid receptor genetics. Therefore, appropriate study designs incorporating knowledge of direct drug mediated effects with indirect drug effects, and confounding factors are important in human studies.

Striatum

The nucleus accumbens in the ventral striatum, and the putamen and caudate nucleus in the dorsal striatum, are integral to the rewards network. The striatum, through its connections to the frontal cortex, the orbitofrontal cortex and subcortical limbic regions, regulates cognitive and emotional behavior [69], and modulates motivation and reward [70], and may be susceptible to prenatal drug exposure-related brain network alteration [44, 71–73]. POE is associated with decreased basal ganglia volumes[23], although this finding may be nonspecific and seen with other substance exposure, such as methamphetamine [72]. Few, but not all studies also show reduced basal ganglia volumes persisting into adolescence and correlating with behavioral outcomes [32, 33], suggesting that the long-term impact of POE is modulated by other prenatal drug exposure, postnatal environmental factors and neuroplasticity of the infant brain.

While no studies specifically assess infant striatal structural and functional connections in POE, DTI showed alterations in these structural networks in prenatal methamphetamine exposure [74] and rs-fMRI showed marijuana-specific hypo-connectivity in the caudate to cerebellum, fusiform gyrus and inferior occipital networks in infants[44]. In older children, similar aberrant functional connectivity of the caudate and right inferior frontal cortex was noted with prenatal cocaine exposure [75]. These are concordant with studies in adults with OUD showing microstructural and functional alterations of the ventral striatal connections to the subcortical and cortical reward network regions [71, 76–79].

Rodent studies provide further insight into the effect of POE on the striatum, showing reduced striatal nerve growth factor [73], decreased neuronal migration, increased apoptosis [80], and abnormal dopamine D1 receptor expression[81, 82], all of which impact drug-seeking and drug-taking behavior in later life [82]. These striatal morphometric, microstructural, and functional alterations in prenatal drug exposure suggest that striatal neural circuits should specifically be investigated in human POE as they may have the potential to influence long-term addiction behaviors.

Amygdala

The amygdala is integral in emotion, stress, motivation, and behavioral responses. Early insult to the developing amygdala and its connections are associated with adverse neurobehavioral outcomes in infancy [66, 83, 84].

In our pilot study of prenatal opioid-exposed infants, we found differences in amygdalar functional connectivity in multiple brain regions (Table 1) [30]. Of these regions, one of the areas with bilateral overlapping higher right and left amygdalar connectivity was to the medial prefrontal lobes in infants with POE compared to healthy controls (Figure 2) [30]. This is similar to other infant studies showing higher functional connectivity of the amygdala to the orbital frontal cortex with prenatal polydrug exposure [44], and to both

frontal lobes with prenatal cocaine exposure [39]. This higher amygdala to frontal connectivity in prenatal drug exposure is hypothesized to be a failure of normal amygdala suppression by the prefrontal cortex [39].

We also identified lower amygdala to anterior insula resting state functional connectivity in infants with POE compared to control infants in our pilot study[30]. This is in line with other adult studies OUD where decreased functional connections of the amygdala to the insula, frontal lobe, and deep gray structures were identified, some in a dose dependent fashion [71, 76–79, 85–87]. White matter microstructural disruptions may underlie some of these alterations in functional connection [79]. In adult OUD, these structural and functional amygdalar network alterations are shown to be associated with addiction related behaviors, especially impulsivity [71, 85, 86], and therefore emerge as an area requiring further assessment in infants with POE.

Mechanistically, POE disrupts the endogenous opioid system in the amygdala in rodent studies[20]. In addition to substance exposure, maternal stress, depression, and inflammation that are frequently associated, may also impact amygdalar function and outcomes; it is important to account for these known confounders when evaluating specific drug-related effects on the amygdala and neurodevelopmental outcomes [66, 83, 84].

Thalamus

The thalamus provides relay of sensory information, emotional control and emotional-sensory integration and fine motor control through connections to the cortex, reticular formation, striatum and hypothalamus; drug-related insults during the development could negatively affect these functions [88, 89]. An early study of the infant thalamus using head ultrasound showed increased growth of thalamic cross-sectional area in the first six months of life in methadone exposed infants compared to non-drug exposed infants (<https://archives.drugabuse.gov/sites/default/files/monograph67.pdf>) [28]. Another study in fetuses also showed an enlargement of the cross sectional area of the thalami on fetal ultrasound at 18–22 weeks gestation [27]. These findings have yet to be validated by quantitative volumetric analysis that can now be performed with fetal and neonatal MRI.

Decreased thalamic volumes are also shown in adolescents and young adults with prenatal opioid and polydrug exposure, correlating with general cognitive function [34, 35]. However, this was not seen in another study when prenatal opioid exposed children were imaged at younger school entry age [33]. Different reasons for this apparent contradictory finding may be related to several factors, including differences in prenatal polydrug exposure or differences in postnatal environment, nutrition and other societal factors that can also influence brain growth and maturation. Therefore, further investigations focused on studying thalamus in the developing infant and fetal brain may provide more critical information on the developmental alterations in this critical region before the effect of other postnatal environmental influences. Such early infant neuroimaging studies in infants with cocaine exposure show thalamic hypoconnectivity to the motor cortex and correlations of these thalamo-frontal and thalamo-motor connectivity with cognitive, fine motor and composite motor scores in early infancy [88]. Persistent decreased thalamic volumes are shown in older children with prenatal cocaine or polysubstance exposure [35, 90] and are associated with

impulsivity [91]. Decreased thalamic AD on DTI is seen in adolescents with prenatal tobacco exposure [92].

Insula

The insula is highly connected with the amygdala, thalamus, ventral striatum, limbic system, and the premotor cortex; and plays a multifaceted role in sensory, somatomotor, visceroreceptive and visceromotor, speech, cognition, and emotional integration and control and is a part of the salience and reward networks [39, 93, 94]. No studies specifically examine the effect of POE on the infant insula, but prenatal polysubstance exposure revealed increased insular functional connectivity to the frontal cortex, and decreased connectivity to the sensorimotor cortex [39]. Insular connectivity to the cerebellum is also decreased with prenatal marijuana exposure [44]. Adults with OUD also show significantly decreased functional connectivity and decreased white matter FA of the anterior insular connections [76–79], and increased gray matter density in the insular cortex, with these disruptions linked to addictive behaviors [95]. Because insular networks are rapidly maturing in infancy, investigations of these networks may provide information regarding risk of neurodevelopmental consequences [62, 64].

Frontal cortex

As described above, structural and functional connections of several regions of the frontal cortex to the striatum, amygdala, and thalamus are altered in drug exposure [39, 96]. Specifically, the ventromedial prefrontal, orbitofrontal, dorsolateral prefrontal and anterior cingulate cortices are implicated in drug mediated effects [76, 87]. These regions are involved in the salience, executive function, and working memory networks [97, 98]. Not surprisingly, structural and functional disruptions in executive function and working memory networks are identified in adolescents with POE [40, 99]. Other studies in adolescents with prenatal drug exposure show altered frontal lobe functional connections associated with poor working memory function [100, 101] and disturbances in inhibitory control [75, 102]. In addition to network alterations, morphometric studies in adolescents with opioid and polysubstance use are associated with decreased frontal lobe cortical thickness in several regions including the anterior cingulate, orbitofrontal, precentral gyrus, which were also associated with cognition, behavior and attention [32, 35]. Interestingly another study of brain morphometry in adolescents with opioid and polysubstance use showed marginally thick middle frontal gyrus [37]. In the same study, frontal cortical thickness associated with prospective memory ability although there were no significant differences in functional ability between drug exposed and non-drug exposed adolescents [37].

Infants and children with prenatal polysubstance exposure show reduced prefrontal gray matter volume, which may underlie the frontal functional connectivity alterations [39, 96, 103]. Again, these gray matter reductions in frontal regions may persist in adolescence manifesting as attention and social problems, and increased impulsivity [32, 91, 103]. Similar decreases in prefrontal lobe gray matter density [104, 105] and alteration of the frontal network connections underlie the addiction related behavioral issues in opioid-using and abstinent adults [71, 86, 87].

Hippocampus

The role of the hippocampus in drug exposure is extensively studied in animal models, with scarce evidence in human prenatal substance exposure. Studies in adolescents with prenatal opioid and polydrug exposure show increased hippocampal volumes [36, 37] in children with opioid and polydrug exposure correlating with poor memory function [36, 37]. In adult OUD, functional connections of the hippocampus are impacted in conjunction with the default mode network [76, 77]. Animal studies show that opioids may influence genetically programmed apoptosis in the hippocampus through their influence on signal-transduction pathways [106] which may explain some of these findings. Hippocampal synaptic plasticity results from POE [107, 108] possibly due to abnormal functioning of the cholinergic [109] or glutamatergic system [110].

White matter tracts

Since oligodendrocytes express opioid receptors, opioid-mediated alterations in oligodendrocyte function may alter myelination, thus disrupting normal brain maturation [111]. In addition to above described alterations other white matter disruptions are described in several brain regions. Infants with prenatal methadone exposure show abnormal increased mean diffusivity (MD) values in the superior longitudinal fasciculus [22], and disrupted microstructure in the internal capsule and inferior longitudinal fasciculi [29]. In school-age children with POE, decreased FA values are evident in the central, inferior and posterior white matter [34, 38], which are the early myelinating regions. Opioid mediated oligodendrocyte neurotoxicity may explain this specific disruption in integrity of early myelinating white matter [45, 46].

Alterations in white matter microstructure in the internal and external capsules, corona radiata, arcuate fasciculus and callosal projections are also noted in prenatal drug exposure to methamphetamine [112, 113] and cocaine [114]. However, these findings are not seen by other researchers [115, 116], suggesting a multifactorial impact, due to a combination of prenatal exposure to other drugs (including tobacco and alcohol) and postnatal environmental factors [115, 116]. In addition, infants' sex may also influence drug related white matter injury [92]. Several adult OUD studies have also shown microstructural alterations the internal and external capsules, corpus callosum, corona radiata, and frontal, temporal and parietal white matter [79, 117–119]. Some of these white matter alterations correlated with accumulated opioid dose, suggesting an opioid-specific mechanism of white matter injury [117]. This is supported by animal studies showing myelin injury in offspring with POE as altered myelin-related protein expression and disruptions of normal myelin sheaths in the corpus callosum [45, 46]. Rodents with POE also reveal microstructural damage (reduced FA) in the corpus callosum and external capsule [120].

Other brain regions and networks

Given the widespread distribution of opioid receptors in the developing brain, POE could affect global brain volumes or other specific brain regions and functional networks [23, 24]. The cerebellar volume may also be independently associated by prenatal drug exposure, as shown by cerebellar white matter volume loss in infants and children with POE [23, 32] and altered cerebellar functional connections to the caudate and insula in prenatal

methamphetamine exposure [44]. Apart from the individual structural and functional networks, prenatal drug exposure may also be associated with alterations in the development and segregation of the brain connectome [121].

Conclusions

In this review, we highlight alterations in brain morphometry and neural circuits that are shown to be associated with prenatal opioid and polysubstance exposure and could therefore be targets for further evaluation in the developing fetal and infant brain. These described alterations in several subcortical structures, cerebellum, cortical brain regions and structural and functional neuronal circuits overlap with regions of brain shown to be altered in adults with opioid use disorder and animal models, suggesting some similarities in the brain regions and neuronal circuits associated with drug exposure, even though different drug types may have different and overlapping mechanisms of actions. However, several of these human studies in POE are performed in older children and adolescents where confounding effects of the childhood environment such as foster care, parental stress, socioeconomic status, childhood nutrition, and childhood adverse life events are difficult to completely adjust for [11, 12]. Imaging in the fetal period or early infancy may overcome some of these confounders and environmental variables; but is still challenged by covariates of polysubstance exposure, maternal and infant genetics and maternal comorbidities [11, 12, 122].

In our review, we found polysubstance exposure, including smoking and alcohol consumption, to be frequent in several studies of POE (Table 1). There is still a lot to learn on how opioids interact with other drugs of misuse, or how these combinations of drugs would influence brain development. Our observations of lack of reproducibility of some of the results in different studies, could partly be explained by the differences in polysubstance exposure. Large multicenter studies would therefore be needed to isolate drug specific effects while controlling or adjusting for covariates [39]. Imaging studies may associate drug exposures with brain developmental alterations but may not be able to identify causal relationships. However, neuroimaging findings may provide an understanding of the developing brain as one part of the puzzle in understanding long-term cognitive and behavioral outcomes, and the risk of future drug misuse.

Other factors that can also confound human studies of POE include other maternal comorbidities that may be present to a greater extent in women with drug use such as maternal education, anemia, malnutrition, stress, anxiety and depression, eclampsia and preeclampsia. Lower socioeconomic status may be associated with certain polysubstance exposures, while geographic boundaries may influence other drug exposures. Therefore, use of appropriate study and control populations would be important when attempting to correct for these covariates [11, 12]. In addition, prematurity and in utero growth restriction (IUGR) are more common in POE and may also act as confounders.

Understanding dose response relationships would be helpful to understand drug related brain alterations but would be difficult to model in human studies for several reasons. Several different opioid drugs may be used, both illegal and legal, or as a part of maternal opioid

replacement therapy. While calculation of morphine equivalent doses may help in comparing the different opioids, this may not adequately explain the different opioid related effects on the brain because of differences in drug pharmacokinetics, opioid receptor subtype sensitivity, and addictive potential exhibited by different opioid drugs. Differences in length and variations of drug exposure during different periods in pregnancy may have differential effects on fetal and infant neurodevelopment. In women not on opioid replacement therapy, relying on maternal history alone for drug type and dose may be inaccurate due to the risk of recall or subject bias. Most importantly, the actual effective opioid exposure to the fetus and developing brain may be variable due to the role of individual maternal and fetal genetic and epigenetic factors that influence opioid pharmacokinetics and pharmacodynamics, which should ideally also be concurrently assessed [5–9].

Significant advances in imaging techniques provide promising tools to understand the effects of POE on the developing brain. In our review of the six published MR imaging studies in infants with prenatal exposure to opioids as the primary drug or drug of choice [22–26, 29] there were no major macrostructural abnormalities on visual inspection but decreased whole brain and regional brain volumes and alterations in white matter networks were associated. Functional network connectivity studies would provide an understanding of yet another aspect of brain development in POE in infants.

Most of the current neuroimaging studies in POE (Table 1) are cross sectional rather than longitudinal. There is a need for longitudinal maternal and infant dyad population studies with comprehensive and rigorous evaluation of multiple genetic, epigenetic, pharmacokinetic, psychological, socio-environmental, pregnancy related comorbidities and opioid exposure to understand risks of long-term adverse cognitive and neurodevelopment and behavioral sequelae, as well as individual response to future opioid exposure and the risk of addiction. Longitudinal neuroimaging studies in POE especially of the developing early fetal and infant brain could provide an insight into neuronal neuroplasticity or compensatory mechanisms that could be a determinant of outcomes. Along with other clinical, environmental and genetic factors, these would provide a better understanding of the impact of maternal opioid use on the variability of outcomes in POE. Eventually these results can help in facilitating early and targeted interventions to improve long-term outcomes in these high-risk infants.

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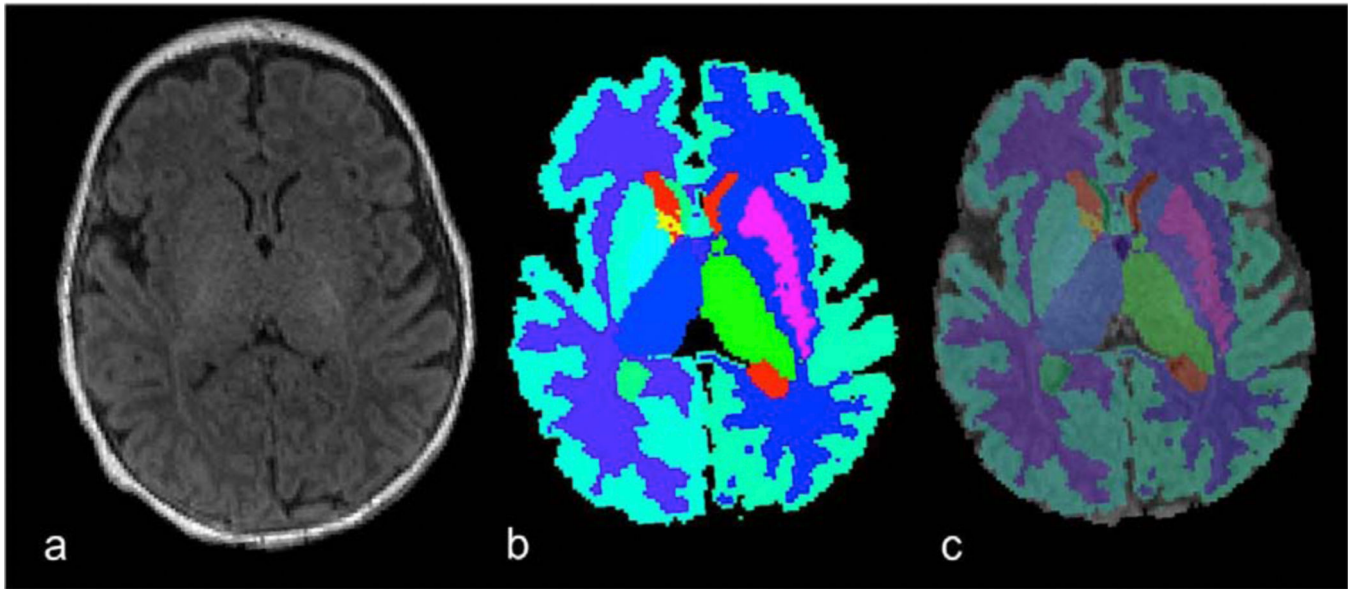


Figure 1. Example of automated segmentation of infant brain T1 weighted image (a) using Infant Freesurfer [50] into several color coded cortical, white matter and subcortical segments (b). The right image (c) shows overlay of the automated segmentation on the skull stripped anatomic T1 weighted image.

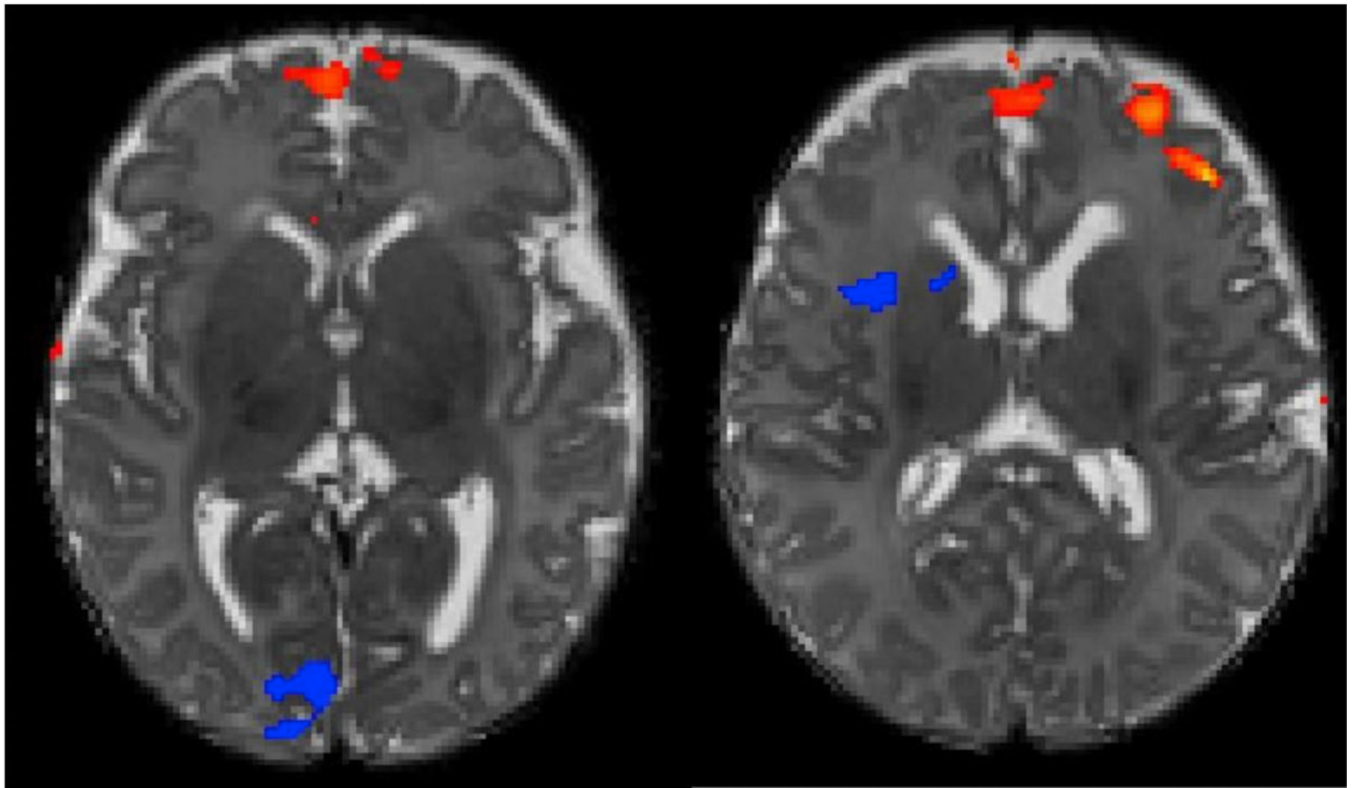


Figure 2.

Representative images from preliminary results of group analysis of resting state functional MRI with seed regions in the right and left amygdala showing regions of significantly higher connectivity in infants with POE compared to control non-drug exposed infants (warm colors) and significant higher amygdala to brain region connectivity in controls compared to infants with POE (cool colors) [30]

Table 1.

MR neuroimaging findings reported in humans with prenatal opioid exposure

Imaging finding	Sample size (total N) and age	Associated clinical behavior	Reference
Macrostructural			
• No structural abnormalities	Subject N: 7 with prenatal exposure to buprenorphine replacement. All had tobacco and benzodiazepine exposure Age: Infants, <2 months age	Not evaluated	Kahila et al. 2007 [26]
• White matter punctate lesions in 40% • Septo-optic fusion anomaly in 10%	Subject N: (40) 20 with prenatal opioid and smoking (3 with street drug exposure) <i>versus</i> 20 non drug exposed infants Age: Infants, 4–8 weeks old	Not evaluated	Merhar et al. 2019 [25]
• Visually detectable abnormality in 35% of clinical brain MRI in prenatal substance exposed children	Subject N: (74) 34 with prenatal opioid and smoking exposure including opioids, alcohol and other substances <i>versus</i> 40 controls without prenatal substance exposure Age: 10–14 year old	Not evaluated	Sirmes et al. 2017 [30]
Morphometric			
• Decreased whole brain volume • Decreased basal ganglia volume with prenatal opioid exposure compared to population values • Decreased cerebellar volume with more than one opioid drug exposure	Subject N: 16 with prenatal opioid exposure (buprenorphine, methadone and/or heroin) 1/3 had polysubstance exposure. 50% had antidepressant exposure <i>versus</i> population control values Age: Infants, 40.9+1.5w	Not evaluated	Yuan et al. 2014 [23]
• Smaller intracranial and brain volumes • Smaller amygdala, nucleus accumbens, putamen, pallidum, brainstem, cerebellar white matter, and inferior lateral ventricles, and thinner cerebellar cortex and thinner cortex of the anterior cingulate and lateral orbitofrontal cortex in polysubstance exposure • Globus pallidus and putamen volumes reduced in the subgroup exposed to opioids	Subject N: (28) 14 with prenatal polysubstance exposure (benzodiazepines, neuroleptics, cannabis, alcohol, cocaine and amphetamine) including 10 with prenatal opioid (heroin) exposure <i>versus</i> 14 non drug exposed controls Age: 9–12 years old at time of MRI	Cortical thickness of the anterior cingulate, the lateral orbitofrontal cortex and nucleus accumbens were associated with ability and questionnaire measures of behavior and attention 2 years prior to scan	Walhovd et al. 2007 [31]
• No volume differences in intracranial volume, putamen, pallidum, caudate, hippocampus, amygdala, thalamus, cerebellar cortex, white matter, callosum	Subject N: (24) 12 with prenatal polysubstance exposure including 8 exposed to prenatal opioids <i>versus</i> 12 non drug exposed controls. Age: 4–5 years old at MRI, visual and neurocognitive testing	No significant difference in neurocognitive function. Significantly lower left eye visual acuity and trend toward lower binocular visual acuity	Walhovd et al. 2015 [32]
• No difference in total brain, cerebral cortex and cerebral white matter volumes. • Volumes of basal ganglia, thalamus and cerebellar white matter reduced in opioid exposed group	Subject N: 16 with prenatal opioid exposure versus age and sex matched controls Age: 10–14 years old at MRI	Not evaluated	Sirmes et al. 2017 [33]
• Decreased whole brain, cerebral cortex, basal ganglia and thalamus volumes in polydrug exposure. • In youth with history of neonatal abstinence syndrome, decreased cerebral cortical thickness, amygdala volume, basal ganglia volume • Decreased cortical thickness in the left precentral gyrus, inferior parietal cortex and right perirolandic region in prenatal drug exposed.	Subject N: 38 with prenatal drug exposure (47% exposed to heroin, 13% alcohol, 11% amphetamines and 100% tobacco among others) versus 44 non-drug exposed (overlaps with populations studied at an earlier age in [23], [31] and [33]) Age: 17–22 years	General cognitive functioning correlated with several imaging features including whole brain and multiple regional brain volumes including the deep gray structures, cortical thickness and cortical area.	Nygaard et al. 2018 [34]
• Larger right and left hippocampal volume in prenatal drug exposure compared to controls after controlling for prenatal	Subjects: (138) 76 with history of prenatal drug exposure (13% exposed to heroin, 54% exposed to heroin and cocaine and	Larger hippocampal volumes associated with	Riggins et al. 2012 [35]

Imaging finding	Sample size (total N) and age	Associated clinical behavior	Reference
alcohol and tobacco exposure and total gray volume. Differences did not persist for the right hippocampus when controlling for early caregiving environment.	33% exposed to cocaine, and several other drugs including tobacco and/or alcohol in 87%) versus 62 non-drug exposed controls Age: Mean 14 years	worse performance on memory task	
<ul style="list-style-type: none"> Larger right and left hippocampal volumes and marginally thick right middle frontal gyrus in prenatal drug exposure 	Subjects: (52) 28 with prenatal drug exposure (heroin and/or cocaine in addition to alcohol and/or tobacco) and 24 without prenatal drug exposure, all from low socioeconomic Age: Mean 15 years	Prospective memory associated with morphometric findings in several brain regions including the right hippocampus, left putamen, bilateral frontal cortices, right pars triangularis, right anterior cingulate, and left precuneus. However, there was no difference between controls and prenatal drug exposed subjects in prospective memory ability.	Robey et al. 2014 [36]
Structural connectivity			
<ul style="list-style-type: none"> Increased mean diffusivity values in the superior longitudinal fasciculus of the brain 	Subject N: (20) 13 exposed to prenatal methadone <i>versus</i> 7 non drug exposed controls Age: Infants, 13–44 days old	Not evaluated	Walhovd et al. 2021 [22]
<ul style="list-style-type: none"> Decreased FA in the internal capsule and inferior longitudinal fasciculi using tract based spatial statistics 	Subject N: (40) 20 exposed to methadone prenatally (including 19 with polysubstance exposure) <i>versus</i> 20 non drug exposed Age: Term infants	Not evaluated	Monnelly et al. 2018 [29]
<ul style="list-style-type: none"> Decreased FA values in the central inferior and posterior white matter 	Subject N: (28) 14 exposed to prenatal opioids <i>versus</i> 14 nonsubstance exposed Age: 8–13-year-old substance exposed 9–10-year-old control	FA, axial diffusion and radial diffusion values correlated with poor neurocognitive function	Walhovd et al. 2010 [37]
Functional connectivity			
Effects of polysubstance (including opioid) exposure: <ul style="list-style-type: none"> Increased functional connectivity (on rs-fMRI) of the left insula to the left frontal cortex and left anterior cingulate Increased functional connectivity of left amygdala to the left prefrontal region Decreased insula-tosensorimotor cortex functional connectivity 	Subject N: (154) 45 with prenatal non-cocaine polysubstance exposure including 15 with opioid exposure; 45 with prenatal cocaine and other polysubstance exposure including 6 with opioid exposure; 64 non drug exposed controls Age: Infants, 2–6 weeks	Not evaluated	Salzwedel et al. 2015 [38]
<ul style="list-style-type: none"> Significant decreased activation in the culmen of cerebellum with visuospatial working memory task compared to control task in polysubstance exposed adolescents Significantly decreased integrated global efficiency in the visuospatial working memory task network in PSE 	Subject N: (47) 27 with prenatal polysubstance exposure including 14 with heroin exposure <i>versus</i> 20 controls without prenatal substance exposure Age: 12–15 years old at MRI	Reaction time correlated with accuracy on the visuospatial working memory task in controls but not in polysubstance exposure	Schwitzer et al 2015 [39]
<ul style="list-style-type: none"> Increased activation in prefrontal cortical regions in opioid-exposed group when performing cognitively demanding working memory-selective attention task 	Subject N: (23) 11 prenatal opioid exposed and 12 controls Age: 10–14 years	Impaired performance of working memory-selective attention task in prenatal opioid exposed subjects	Sirnes et al. 2018. [40]
<ul style="list-style-type: none"> Higher resting state functional connectivity between the right and left amygdala and several cortical regions including medial prefrontal regions, temporal lobes, and parietal lobes in prenatal opioid exposed infants compared to controls Higher resting state functional connectivity between left amygdala and 	Subject N: (22) 10 prenatal opioid exposed (4 with prenatal polysubstance exposure) and 12 controls Age: Infants, <2 months age	Not evaluated	Radhakrishnan et al. 2020 [30]

Imaging finding	Sample size (total N) and age	Associated clinical behavior	Reference
insula, medial temporal lobe, occipital lobe and cerebellum in controls compared to opioid exposed			

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