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RECEIVED 16 April 2025

ACCEPTED 31 July 2025

PUBLISHED 20 August 2025

CITATION

Shah L, Yoon CD, LaJeunesse AM,
Schirmer LG, Rapallini EW, Planalp EM and
Dean DC (2025) Prenatal substance exposure
and infant neurodevelopment: a review of
magnetic resonance imaging studies.
Front. Hum. Neurosci. 19:1613084.
doi: 10.3389/fnhum.2025.1613084

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Prenatal substance exposure and infant neurodevelopment: a review of magnetic resonance imaging studies

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Amid the ongoing global substance use crisis, prenatal health research has increasingly focused on the impact of both licit and illicit substance use on fetal development, and in particular brain development. Magnetic resonance imaging (MRI) has become a critical non-invasive tool for investigating how such exposures influence the developing brain. In this review, we summarize findings from 25 peer-reviewed studies that leverage structural, functional, and diffusion MRI to examine the effects of prenatal exposure to alcohol, opioids, methamphetamines, cocaine, nicotine, or cannabis. Particular attention was given to studies that paired infant MRI data with developmental outcomes. Existing research has implicated cortical and sub-cortical gray and white matter regions across substance exposures, with associations between MRI findings and developmental outcomes in infancy. We identify key limitations in the existing literature, including small sample sizes, lack of control for prematurity, sex, co-occurring exposures, limited developmental assessment, and insufficient longitudinal follow-up. We highlight the need for future research linking early neuroimaging findings to developmental outcomes, particularly in large, diverse, and nationally representative cohorts. Such work is essential for informing evidence-based policies, clinical guidelines, and targeted interventions for families impacted by prenatal substance exposure.

KEYWORDS

prenatal substance exposure, magnetic resonance imaging, infant brain development, diffusion MRI, structural MRI, functional MRI, developmental outcomes

Introduction

There is rising concern surrounding substance use (defined here as use of licit or illicit substances of abuse), with prenatal substance exposures posing particular public health concern (Narkowicz et al., 2013). For example, in the United States, alcohol consumption among pregnant individuals has been reported by the Centers for Disease Control at 13.5%, with a 5.2% rate of binge drinking (Gosdin, 2022). While tobacco use during pregnancy is declining, additional substances of abuse remain a concern due to the opioid crisis and rising rates of cannabis use. In a 2020 U.S. survey, 8% of respondents reported cannabis use, 8% reported nicotine use, 0.4% reported opioid use and 0.3% reported cocaine use during pregnancy, with other stimulant use varying across reports (SAMHSA, 2020). The prevalence of methamphetamine in pregnancy in the U.S. is thought to be close to 0.19% (Young-Wolff

et al., 2022). Worldwide, the prevalence of substance use in pregnancy varies significantly. Specific to alcohol, the prevalence of alcohol use in pregnancy was recently reported to range from 0 to 0.5% in northern Africa and the Middle East to greater than 40% in Russia, Denmark, Belarus, and Ireland (Popova et al., 2017). Prenatal substance use prevalence varies across nations likely due to a number of factors, including cultural norms, reporting practices, healthcare access, and stigma (Chiandetti et al., 2017). However, the widespread use of substances prenatally underscores the critical relevance of studying the effects of prenatal substance exposures (Tavella et al., 2020), which may pose concern for both short-term and long-term child development.

Prenatal substance exposure poses significant risks to fetal development. Different substances may exert unique effects on the developing fetus, but a shared concern is their potential to disrupt critical processes in brain development that can have enduring consequences. Prenatal substance use is associated with clinically recognized specific effects; for instance, fetal alcohol spectrum disorder (FASD) (Riley et al., 2011) may be seen in infants with alcohol exposure and neonatal opioid withdrawal syndrome (NOWS) is associated with prenatal opioid exposure (Conradt et al., 2019). However, long-term sequelae are also associated with prenatal substance exposures, specifically exposure to alcohol, nicotine or tobacco, cannabis, or methamphetamine, include developmental delays, deficits in cognition and attention, issues with impaired visuospatial working memory, and mental health challenges, which have been reported throughout childhood and adolescence (De Genna et al., 2022; Ernst et al., 2001; Harst et al., 2021; Lambert and Bauer, 2012; Ross et al., 2015; Townsel et al., 2021). The reported long-term neurodevelopmental sequelae of substance exposures reflects vulnerability in the developing brain to substances of abuse. Because each substance interacts differently with fetal biology (Bailey and Diaz-Barbosa, 2018; Ortigosa et al., 2012), outcomes may depend on several factors, including dosage, timing of exposure, and the presence of other environmental or substance-related exposures (Ross et al., 2015). Understanding how substance use exposure potentially disrupts neurodevelopment requires a close examination of the complex biological processes that occur in utero. Specifically, identifying the mechanisms through which substances alter fetal brain development can help explain the wide variability in outcomes in affected infants and guide strategies for early detection and intervention.

Impact of substance exposures on fetal neurodevelopment

The time from gestation through the first year of life is a critical period during which the brain matures most rapidly (Tierney and Nelson, 2009), and insults during this critical period have been associated with enduring developmental consequences (Andersen, 2003; Matthews et al., 2018; Raschle et al., 2012). Subcortical neurons begin forming as early as 10 weeks of gestation, and white matter myelination, axonal synaptogenesis, dendritic arborization, and formation of functional connections occur during the second and third trimesters (Adams-Chapman, 2009; Dufford et al., 2021; Ouyang et al., 2019; Stiles and Jernigan, 2010). The timing of substance exposure may thus yield different neurodevelopmental signatures, with additional consequences if the exposure is associated with preterm birth (Adams-Chapman, 2009).

Various neurotransmitter systems play fundamental roles in guiding neuronal proliferation, migration, synaptogenesis, and circuit refinement during critical periods of fetal brain development. During gestation, substances may cross the placenta through diffusion and transport mechanisms, affecting key processes and leading to alterations in these neurotransmitter systems, potentially altering neural organogenesis, growth, and/or function, depending on target receptors (Eléfant et al., 2020). Disruptions to these systems can therefore have cascading effects on neural architecture. Specifically, in the developing fetus, substance exposures may be associated with decreased dopamine synthesis and release (cocaine, methamphetamine, and opioids, Boggess and Risher, 2022; Little et al., 2021; Tomášková et al., 2020), a compensatory up-regulation of dopamine D1 and D2 receptor density (cocaine and opioids, Boggess and Risher, 2022; Little et al., 2021), altered dopamine release and serotonin turnover (nicotine, Little et al., 2021), and disrupted glutamatergic and GABAergic neuron development and signaling (alcohol, cannabis, and nicotine, Little et al., 2021). For example, GABA and glutamate not only act as neurotransmitters but also as trophic factors that regulate early neuronal differentiation and cortical patterning (Egbenya et al., 2021; Ji et al., 2024). Substance exposures are also linked to changes in glucocorticoid receptor expression, inflammatory cytokine production, and HPA axis functioning (Frank et al., 2011; Franks et al., 2019; Salisbury et al., 2009). Additionally, substance exposure may be linked to physiological alterations within the pregnant individual, including alterations to placental vasculature and physiology (Ortigosa et al., 2012), that impact the delivery of oxygen and nutrients to the fetus and further affect neurodevelopment (Rees and Harding, 2004). This brief overview necessarily simplifies a highly complex and dynamic set of neurodevelopmental processes, yet highlights the potential mechanisms through which prenatal substance impacts the developing fetus. The neurobiology of prenatal substance exposure is further described in Ortigosa et al. (2012) and Ross et al. (2015).

Understanding the shared and unique neurochemical pathways of substances of abuse is essential to interpreting their effects on the developing brain. While each substance of abuse exhibits distinct pharmacologic profiles, there are shared mechanisms between neurochemical pathways (US Department of Health and Human Services, 2016). Depressants, such as alcohol, interact with neurotransmitter systems in the brain, including GABA, glutamate, and other systems to produce a depressant effect (Heilig and Egli, 2006). Opioids bind to opioid receptors in the brain, leading to dopamine release from the nucleus accumbens (Wang, 2019). Relatedly, stimulants including cocaine and methamphetamine increase the amount of dopamine and norepinephrine in the brain's reward circuitry (Koob, 1992). Although nicotine acts on nicotinic acetylcholine receptors and cannabis interacts with cannabinoid receptors, these substances also share the ultimate effect of activating the dopamine system throughout the brain (Chayasirisobhon, 2021; Miller and Picciotto, 2016). While the targets of substances of abuse differ, altered neurotransmitter function within reward circuitry across substance exposures may contribute to overlapping substance exposure profiles.

The differential neurodevelopmental effects of prenatal substance exposure have been studied using cellular and animal models, which have detailed the pharmacologic actions, neurotransmission effects, implicated regions, and behavioral effects of various substance exposures (Eiden et al., 2023). Animal studies have reported concentration-dependent effects of substance exposures, regions

impacted across substance exposures (including the basal ganglia and reward network) and concentration-dependent cytotoxicity in offspring exposed to substances prenatally (Eiden et al., 2023; Kuhn et al., 2019; Lovinger and Alvarez, 2017; Ross et al., 2015). This foundational work provides potential biological mechanisms to explain observed relations between prenatal substance exposure and neurodevelopmental outcomes in humans, using mechanistic experimental models that are not feasible in humans (Ross et al., 2015). To translate findings from animal models to clinical populations, magnetic resonance imaging (MRI) may be used as a non-invasive, high-resolution method for studying early human brain development (Ouyang et al., 2019).

MRI studies of prenatal substance exposure

Although several reviews have examined the use of MRI to study individuals exposed to substances in utero (Donald et al., 2015a; Irner, 2012; Sanjari Moghaddam et al., 2021), these often focus on brain changes observed later in childhood and adolescence, overlooking the earliest manifestations of brain disruption following prenatal substance exposure. Two reviews have focused specifically on the neonatal and infant periods, when the brain is rapidly developing and may be particularly vulnerable to disruption (Dufford et al., 2021; Pulli et al., 2018). Another extended the scope to include functional neuroimaging and electroencephalography studies from infancy to early adulthood, with an emphasis on non-alcohol substance exposure (Morie et al., 2019). These works synthesize structural and functional MRI findings in infants with a wide range of prenatal exposures, including alcohol, nicotine, illicit substances, pharmaceuticals, maternal obesity, and inflammatory conditions. While they highlight alterations in brain volume, microstructure, and functional connectivity, they offer limited insight into how these changes relate to early developmental outcomes.

Building upon these prior reviews, we provide a targeted overview of the effects of prenatal substance exposure on brain development using infant MRI research, focusing on studies performed during the neonatal and infant periods and examining how neuroimaging findings relate to immediate developmental outcomes a dimension that has received limited attention in prior work. Unlike previous reviews, which either emphasize older developmental stages (Donald et al., 2015a; Sanjari Moghaddam et al., 2021) or include a broader selection of neuroimaging modalities (e.g., EEG and fNIRS in Morie et al., 2019), our review is the first to examine findings from structural, functional, and diffusion MRI modalities specifically in infants during the earliest postnatal stages. We excluded other functional modalities such as EEG and fNIRS to maintain a consistent focus on MRI-based methodologies, which provide both high spatial resolution and multi-modal anatomical and functional insights into early brain development (Dubois et al., 2021). In narrowing our scope, we bridge a critical gap in the literature and offer a foundation for identifying neurobiological markers that could inform intervention efforts in the earliest postnatal stages.

Methods

Search strategy

The literature search for this review occurred on October 12th, 2024, covering papers that were published between January 1st, 2000 and

October 12th, 2024. The following inclusion criteria were used to select studies: (a) be empirical and published in a scholarly, peer-reviewed journal in English; (b) include human infants from gestation to 1 year old; (c) include a group exposed to one or more of the 6 most commonly used substances of abuse during gestation (SAMHSA, 2020), including alcohol, nicotine, opioids, cocaine, methamphetamine, or cannabis; and (d) utilize an MRI modality. Treatment-related studies were included if they met inclusion criteria a-d and reported relationships between substance exposure and brain MRI findings in alignment with our goal of summarizing MRI findings associated with prenatal substance exposure. While we were interested in reported relationships between MRI signatures and developmental outcomes, developmental assessment was not an inclusion criterion as we were interested in substance use's effects on the brain directly as well as immediate developmental outcomes. Exclusion criteria included case studies, review articles, non-English articles, articles that did not meet all inclusion criteria (age, prenatal substance exposure, and MRI), and non-human studies.

The literature search was conducted across Academic Search Premier, ERIC, MedLine, PsycArticles, PsycINFO, and PubMed by the first author (LS), with the initial search We searched using the following keywords: ("neonat*" OR "newborn" OR "infant" OR "prem*" OR "bab*") AND ("substance" OR "drug" OR "alcohol") AND ("MRI" OR "magnetic resonance imaging" OR "magnetic" OR "resonance" OR "imaging"). Filters were applied to limit results to peer-reviewed, empirical studies published in English, excluding case studies and review articles. The initial search yielded a total of 3,544 articles.

Study selection

Following duplicate removal, the titles and abstracts of the 3,356 articles were screened for eligibility by the first author (LS), leading to the removal of 3,330 articles based on the inclusion and exclusion criteria. The remaining 26 manuscripts were assessed by one of EGR or LGS, with additional review by LS, with 4 additional articles excluded upon in-depth review. The manuscript references of the remaining 22 articles were reviewed by EGR, LGS, and/or LS, and 3 additional articles were identified for inclusion based on bibliography review. The search process led to 25 articles deemed appropriate for inclusion in this review. During manuscript preparation, all included articles were approved by EWR, LGS, and LS, with no discrepancies in article inclusion decisions between authors.

Data extraction

Relevant information for each study included the primary substance exposure of interest, sample sizes of the exposed and control groups, sample age range, MRI techniques and parameters, MRI regions of interest (ROIs), developmental measures, and the main reported outcomes.

Results

This review includes 25 studies published between 2009 and 2023 that investigated prenatal exposure to alcohol ($n = 7$), opioids ($n = 7$),

methamphetamines ($n = 4$), cocaine ($n = 2$), nicotine ($n = 2$), cannabis ($n = 1$), or polysubstance exposure ($n = 2$). While some studies included non-focal substance exposures as controls, only those examining the unique effects of multiple substances were included in the polysubstance exposure category. The imaging modalities employed were structural MRI (T1-, T2-, and proton density-weighted; $n = 9$); resting-state functional MRI (rsfMRI; $n = 9$); and diffusion tensor imaging (DTI), including probabilistic tractography, tract-based spatial statistics (TBSS), and region-of-interest methods ($n = 7$). See [Tables 1–7](#) for details from each of the 25 reviewed studies.

Alcohol

The 7 studies that investigated prenatal alcohol exposure are listed in [Table 1](#). The number of exposed infants from each study ranged from 11 to 50, all assessed within the first 7 weeks of life. All data were collected in Cape Town, South Africa as part of a large child health study. Although cohort overlap could not be precisely determined, substantial duplication across studies is likely. Collectively, data on alcohol use during pregnancy was associated with disrupted white matter maturation in cortical regions such as the superior longitudinal fasciculus and cerebellar regions ([Donald et al., 2024](#); [Taylor et al., 2015](#)), reduced subcortical, corpus callosum, and basal ganglia volumes ([Donald et al., 2015b](#); [Jacobson et al., 2017](#); [Warton et al., 2021](#)), and elevated resting state functional connectivity (rsFC) in somatosensory, motor, occipital, brainstem, and subcortical networks in alcohol-exposed infants in the first weeks of life ([Donald et al., 2016](#); [Roos et al., 2021](#)). Brain structure and microstructure changes were associated with abnormal neonatal behaviors at birth ([Donald et al., 2015c](#)) and were linked to lower intelligence at 12 months ([Warton et al., 2021](#)), with some evidence suggesting that choline supplementation may partially mitigate these effects ([Warton et al., 2021](#)).

Opioids

Seven studies examined prenatal opioid exposure (see [Table 2](#)), including a total of 174 exposed infants across separate cohorts. Two of these studies reported brain imaging findings in methadone-exposed infants. All data was collected prior to 9 weeks of life. None of the included studies examined behavioral outcomes associated with brain imaging findings. Overall, these findings suggest that opioid exposure is associated with heterogeneous white matter alterations across cortical regions ([Monnelly et al., 2018](#); [Walhovd et al., 2012](#)), disrupted subcortical volumes ([Merhar et al., 2021](#); [Yuan et al., 2014](#)), and abnormal functional connectivity in reward-related brain networks ([Jiang et al., 2022](#); [Liu et al., 2022](#); [Radhakrishnan et al., 2021](#)), with possible attenuation in the context of medication for opioid use disorder (MOUD) therapy ([Liu et al., 2022](#)). Importantly, no literature to our knowledge has compared infant neuroimaging findings in opioid exposure with developmental assessments.

Methamphetamine

Four studies examined the effects of prenatal methamphetamine exposure on early brain development, with study cohorts of

methamphetamine exposed infants ranging from 11–36 infants (see [Table 3](#)). Three studies included overlapping cohorts. Initial imaging was conducted within the first 9 weeks of life, with some longitudinal data extending to 16 weeks of life ([Chang et al., 2016](#)). Studies included both term (>37 weeks GA) and preterm (<37 weeks GA) infants. One study compared methamphetamine exposure (with or without tobacco exposure) to tobacco exposure; this study was included in the methamphetamine category rather than the polysubstance category given the focus on methamphetamine over and above the use of tobacco, rather than on tobacco alone. Overall, prenatal methamphetamine exposure is associated with smaller subcortical volumes in the basal ganglia and hippocampus ([Warton et al., 2018a](#)) and disrupted white matter microstructure in commissural, association, and projection regions ([Chang et al., 2016](#); [Warton et al., 2020](#); [Warton et al., 2018b](#)). Exposure was associated with delayed active muscle tone development at birth which normalized in early infancy ([Chang et al., 2016](#)). One longitudinal study reported sex-specific findings, including persistently disrupted microstructure in the anterior corona radiata in methamphetamine exposed females, and disrupted microstructure in the superior and posterior corona radiata in methamphetamine exposed males that normalized by 3 months ([Chang et al., 2016](#)).

Cocaine

Two studies within the same cohort ranging from 73 to 88 exposed infants (with likely overlap between study cohorts) examined relationships between prenatal cocaine exposure and brain development in infants less than 6 weeks of age (see [Table 4](#)). Together, these findings suggest that prenatal cocaine exposure is associated with both decreases in cortical gray matter volumes ([Grewen et al., 2014](#)) and altered functional connectivity between the thalamus and cortical regions, with early evidence of cognitive and motor developmental delays in exposed infants ([Salzwedel et al., 2016](#)). Altered thalamo-cortical connectivity was associated with lower cognitive, fine motor, and composite motor scores at 3 months in exposed infants, suggesting a relationship between neonatal functional connectivity and development in exposed infants ([Salzwedel et al., 2016](#)).

Nicotine

Two studies examined the effects of prenatal nicotine exposure on brain development in a total of 93 preterm infants, all born before 32 weeks GA. No included studies assessed behavioral outcomes in relation to imaging findings (see [Table 5](#)). Overall, these studies indicate that prenatal nicotine exposure is linked to smaller frontal and cerebellar brain volumes ([Ekblad et al., 2010](#)) and diffuse white matter abnormalities ([Mahabee-Gittens et al., 2023](#)) in preterm infants. However, there is a lack of data on term-born infants, non-tobacco nicotine exposures, and associations with developmental outcomes.

Cannabis

Only 1 study reported associations between cannabis exposure and brain development in a sample of 43 exposed term (> 36 weeks

TABLE 1 Alcohol exposure: summary of main findings of the included studies (n = 7), including MRI and developmental outcomes.

Reference and Cohort	Sample n exposed/control	Sample age at imaging	MRI technique and parameters	Brain regions	Developmental outcome and age at testing	Main reported outcomes
Alcohol						
Donald et al. (2015c) Drakenstein Child Health Study, Univ. of Cape Town	28/28 Excluded participants with positive urine screening at 28–32 weeks gestation for non-alcohol drugs of abuse Alcohol use quantified as at least 2 times weekly or 2 or more drinks per occasion in at least 1 trimester	2–4 weeks postnatal (infants born < 36 weeks gestation excluded)	DTI (whole brain TBSS and regions of interest) FA, MD, AD, RD	Association fibers, brainstem tracts, projection fibers, commissural fibers	Dubowitz Behavior and Abnormal Signs Subscale Age: 2–4 weeks postnatal	Alcohol-exposed infants showed lower AD in the right superior longitudinal fasciculus. Lower FA in the right inferior cerebellar peduncle in exposed infants was positively associated with behavioral subscale scores and increased MD in the right inferior cerebellar peduncle was negatively associated with behavioral subscale scores.
Donald et al. (2016) Drakenstein Child Health Study, Univ. of Cape Town	13/14 Excluded participants with positive urine screening at 28–32 weeks gestation for non-alcohol drugs of abuse Alcohol use quantified as at least 2 times weekly or 2 or more drinks per occasion in at least 1 trimester	2–4 weeks postnatal (infants born < 36 weeks gestation excluded)	Resting-state functional connectivity Seed-based functional connectivity	Sensorimotor intrinsic functional connectivity networks	Dubowitz Behavior and Abnormal Signs Subscales Age: 2–4 weeks postnatal	Alcohol exposure was associated with higher connectivity between somatosensory, motor, brainstem/thalamic, and striatal intrinsic networks. Exposed and control groups showed no differences in the Dubowitz Subscales.
Donald et al. (2015b) Drakenstein Child Health Study, Univ. of Cape Town	28/45 Excluded participants with positive urine screening at 28–32 weeks gestation for non-alcohol drugs of abuse Alcohol use quantified as at least 2 times weekly or 2 or more drinks per occasion in at least 1 trimester	2–4 weeks postnatal (infants born < 36 weeks gestation excluded)	T2-weighted gray matter volumes Regional volumes	90 gray matter regions of interest	Dubowitz Behavior and Abnormal Signs Subscales, Bayley Scales of Infant and Toddler Development (BSID) Age: 2–4 weeks postnatal (Dubowitz), 6 months (BSID)	Alcohol exposure was associated with smaller overall gray matter volume and smaller left hippocampal, bilateral amygdala, and left thalamic volumes in exposed infants. Exposed infants with larger regional volumes in the temporal and frontal lobes had higher scores on both developmental scales.
Jacobson et al. (2017) Drakenstein Child health Study, Univ. of Cape Town	32/11 Participants divided into heavy/binge-drinking (14 or more drinks/weeks or 4 or more drinks per occasion) and little-to-no exposure (not meeting heavy/binge-drinking criteria)	6–40 days postnatal, corrected for GA if born < 37 weeks GA	T1-weighted and Proton-density brain volumes Regional brain volume	Corpus callosum	N/A	Alcohol-exposed neonates had smaller corpus callosum volumes. Controlled for prenatal exposure to smoking, cannabis, and methamphetamine.
Roos et al. (2021) Drakenstein Child Health Study, Univ. of Cape Town	11/14 Alcohol use quantified as more than 1 standard drink per week or 2 + binge drinking episodes (4 + drinks per occasion) during pregnancy	2–4 weeks postnatal (infants born < 36 weeks gestation excluded)	Resting-state fMRI Functional connectivity	Global functional hub arrangement and regional connectivity across the whole brain	N/A	Exposed neonates had temporal and limbic hubs within global functional networks, while control infants had more distributed networks. Regional networks of exposed neonates showed predominant connectivity in subcortical and occipital regions, while networks of control neonates showed predominant connectivity in parietal and occipital regions.

(Continued)

TABLE 1 (Continued)

Reference and Cohort	Sample n exposed/control	Sample age at imaging	MRI technique and parameters	Brain regions	Developmental outcome and age at testing	Main reported outcomes
Taylor et al. (2015) Drakenstein Child Health Study, Univ. of Cape Town	11/20 Excluded participants with methamphetamine or cocaine use. Minimal cannabis use was allowed. Alcohol use quantified as 4 or more drinks on at least one occasion or 14 + drinks/week.	38–44 weeks GA* *One infant scanned prior to 38 weeks	DTI probabilistic tractography	Transcallosal pathways, cortico-spinal projection fibers, and cortico-cortical association fibers	N/A	Alcohol exposure was associated with lower AD and MD. All white matter tracts analyzed, with the strongest associations in the medial and inferior white matter. Controlled for tobacco smoking.
Warton et al. (2021) Drakenstein Child Health study, Univ. of Cape Town	50%/0 *N = 27 infants of birthing parents randomized to receive high-dose choline supplementation Alcohol use quantified as at least 2 standard drinks / day or two or more binge drinking episodes.	1–7 weeks postnatal (infants excluded if < 32 weeks GA)	Structural MRI with multi-echo FLASH sequence Regional volumes	Caudate nuclei, putamen, hippocampus, cerebellar hemispheres, cerebellar vermis, corpus callosum	Fagan Test of Infant Intelligence Age: 6.5 months, 12 months	Choline-treated exposed infants showed larger bilateral thalamic, bilateral caudate, right putamen, and corpus callosal volumes. Higher maternal choline adherence was positively associated with these brain volumes. Larger right putamen and corpus callosal volumes in choline-supplemented infants were associated with higher recognition memory at 12 months. Controlled for cannabis and tobacco use.

The Dubowitz is a validated scale for the motor and behavioral states in newborns, which includes an 'abnormal signs' cluster that evaluates for posture, tremor, and startle ([Dubowitz et al., 2005](#)). Fagan Test of Infant Intelligence is a narrow-band test validated to identify impairments in attention, reaction time, recognition memory, and processing speed associated with alcohol exposed infants ([Fagan, 2012](#)). AD, axial diffusivity; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; TBSS, Tract-based Spatial Statistics. N/A = not applicable.

GA) infants (see [Table 6](#)). This work revealed cannabis-associated reductions in caudate and insular connectivity with the cerebellum, occipital regions, and fusiform regions in exposed infants ([Grewen et al., 2015](#)). No work to our knowledge has examined relationships between brain imaging findings, such as those reported in [Grewen et al. \(2015\)](#), and developmental outcomes in infancy.

Polysubstance exposure

Two studies within the same cohort of term and preterm infants examined the effects of polysubstance exposure on infant brain development, with study cohorts ranging from 73–75 exposed infants with likely overlap between study samples (see [Table 7](#)). Together, these findings suggest that polysubstance exposure during gestation contributes to widespread disruptions in functional connectivity ([Salzwedel et al., 2020](#); [Salzwedel et al., 2015](#)) and may increase risk for early developmental delays, particularly in language and motor domains ([Salzwedel et al., 2020](#)).

Discussion

Overview of findings

Current evidence highlights substance-specific differences in early brain development between infants with and without prenatal substance exposure. This review examined neuroimaging differences associated with prenatal exposure and explored how these imaging signatures relate to developmental outcomes, where such associations were reported. Across studies, we identified substance-related associations with brain structure and function, including volumetric alterations, microstructural differences, and variations in rsfMRI. These findings spanned cortical and subcortical gray and white matter regions, including fronto-limbic and reward networks, motor regions including the cerebellum and brainstem, hippocampus, thalamus, basal ganglia, and white matter relay tracts.

MRI signatures of prenatal substance exposure

Research points to differences between substance-exposed infants and non-exposed infants in regional volumes measured using structural MRI, microstructural markers of brain maturity as measured by diffusion MRI techniques, and regional and global connectivity patterns studied using rsfMRI techniques. [Figure 1](#) summarizes regions implicated by neuroimaging data across substance exposures.

Structural MRI

During early development, both white and gray matter regions exhibit remarkable growth, resulting in volume expansion throughout the brain ([Groeschel et al., 2010](#)). Structural imaging findings among included studies consistently indicate that infants with prenatal substance exposure tend to have smaller gray and white matter volumes and larger cerebrospinal fluid (CSF) volumes across various brain regions. The basal ganglia, thalamus, hippocampus, amygdala,

TABLE 2 Opioid exposure: summary of main findings of the included studies ($n = 7$), including MRI and developmental outcomes.

Reference and cohort	Sample n exposed/control	Sample age at imaging	MRI technique and parameters	Brain regions	Developmental outcome and age at Testing	Main reported outcomes
Opioids (any or multiple)						
Jiang et al. (2022) Univ. of North Carolina at Chapel Hill	21/28 Polysubstance exposure not excluded Opioid exposure quantified by maternal history and/or urine toxicology at time of delivered and confirmed with neonatal toxicology	6 weeks postnatal (infants born < 37 weeks excluded)	Resting-state fMRI Inter-network and intra-network functional connectivity	Fronto-parietal, ventral attention, default mode, dorsal attention, sensorimotor, visual, and limbic edge-centric matrices	N/A	Inter-network connectivity was further disrupted than intra-network connectivity within the visual, subcortical, and default mode networks in exposed infants. The greatest differentiation between control and exposed infants was seen in the amygdala, nucleus accumbens, and inferior temporal gyrus.
Liu et al. (2022) cedars-Sinai medical center	81*/28 * $N = 31$ exposed to methadone or buprenorphine * $N = 53$ exposed to opioids (not methadone or buprenorphine) * $N = 39$ with non-opioid exposure, including cocaine, nicotine, alcohol, cannabis, stimulants, depressants, or other substances Polysubstance exposure not excluded Opioid exposure quantified by maternal history and/or urine toxicology at time of delivered and confirmed with neonatal toxicology	2 weeks postnatal (no correction for prematurity)	Resting-state functional connectivity Heatmap whole-brain functional connectivity analysis	Functional connectivity throughout the brain	N/A	Infants exposed to methadone or buprenorphine had significantly fewer opioid-exposure-related alterations in limbic and frontal connections, compared to infants exposed to opioids (not methadone or buprenorphine). Infants receiving buprenorphine/methadone treatment had residual alterations in some limbic and subcortical connections relative to non-exposed controls.
Merhar et al. (2021) Cincinnati children's hospital	29/42 Polysubstance exposure not excluded Opioid exposure quantified as at least 4 weeks of exposure to any opioid	40–48 weeks postmenstrual age (infants born < 37 weeks excluded)	T2-weighted brain volumes Regional volumes	58 bilateral white and gray matter regions	N/A	Exposed infants had smaller relative volumes of deep gray matter, bilateral thalamic ventrolateral nuclei, bilateral insular white matter, bilateral subthalamic nuclei, brainstem, and cerebrospinal fluid. Exposed infants had larger relative volumes of the right cingulate gyrus white matter and left occipital lobe white matter.
Radhakrishnan et al. (2021) Indiana Univ.	10*/12 *9 participants were undergoing medication assisted treatment (7 buprenorphine, 2 methadone) Polysubstance exposure not excluded Opioid exposure quantified using medical records and self-report questionnaire	<48 weeks corrected GA (infants born < 37 weeks excluded)	Resting-state fMRI Seed-based connectivity	Right/left amygdala, cortical regions, and precuneus	N/A	Opioid-exposed infants had higher connectivity between the bilateral amygdalae and the medial prefrontal cortex, precuneus, and other cortical subregions compared to the control infants, with asymmetries between left and right amygdala connectivity. There were no significant correlations between morphine milligram equivalent dose and connectivity.

(Continued)

TABLE 2 (Continued)

Reference and cohort	Sample n exposed/control	Sample age at imaging	MRI technique and parameters	Brain regions	Developmental outcome and age at Testing	Main reported outcomes
Yuan et al. (2014) Brains, opioids, and babies collaborative group, new south wales	16/0 *N = 14 exposed to methadone, 4 to buprenorphine, and 11 used more than one opioid. Polysubstance exposure not excluded Opioid exposure quantified using self-report. Exposure confirmed with neonatal urine and meconium testing.	Mean age 1.5 weeks postnatal (infants born < 37 weeks excluded)	T1-weighted gray and white matter volumes Regional volumes	Subcortical regions, cerebellum, cortical gray and white matter	N/A	Exposed infants had significantly smaller basal ganglia than the population mean volume and significantly larger lateral ventricles than the population mean volume.
Opioids (methadone)						
Monnelly et al. (2018) Univ. of Edinburgh	20/20 Polysubstance exposure not excluded Methadone exposure quantified as prescription for methadone for opioid use disorder	37–42 weeks postmenstrual age (infants born < 37 weeks excluded)	DTI with tract-based spatial statistics FA, RD, MD, AD	Global white matter skeleton	N/A	Exposed infants had higher median white matter FA and decreased FA in the centrum semiovale, inferior longitudinal fasciculus, and external capsules. Exposed infants had higher RD in the internal capsule and inferior longitudinal fasciculus.
Walhovd et al. (2012) Canterbury Methadone in pregnancy study, Univ. of Oslo, Norway	13/7 Polysubstance exposure not excluded Excluded infants with fetal alcohol syndrome or heavy alcohol usage reported in pregnancy. Opioid exposure quantified as enrollment in methadone therapy for opioid use disorder in the third trimester of pregnancy.	13–44 days postnatal (36–42 weeks GA, no correction for prematurity)	DTI with probabilistic tractography MD	Superior longitudinal fasciculus, inferior longitudinal fasciculus and white matter skeleton	N/A	Higher MD in the inferior longitudinal fasciculus and superior longitudinal fasciculus of exposed infants was found in both the voxelwise and tract-based analyses.

Study cohorts are listed to illustrate cohort overlap across studies. Gestational age (GA) is included where reported. AD, axial diffusivity; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity. N/A = not applicable.

TABLE 3 Methamphetamine exposure: summary of main findings of the included studies ($n = 4$), including MRI and developmental outcomes.

Reference and cohort	Sample n exposed/ control	Sample age at imaging	MRI technique and parameters	Brain regions	Developmental outcome and age at testing	Main reported outcomes
Methamphetamine						
Chang et al. (2016) Univ. of Hawaii at Manoa	68*/71 *N = 36 exposed to methamphetamine/ tobacco, 32 exposed to tobacco Excluded participants with alcohol use > 3 drinks per month during pregnancy, polysubstance use, or cocaine use Methamphetamine exposure quantified by self-report	1–3 sessions between 0–4 months postnatal (no correction for prematurity)	DTI FA, MD, AD, RD	Corpus callosum, caudate, corona radiata, internal capsule, globus pallidus, putamen, thalamus, corticospinal tract	Amiel-Tison Neurological Assessment at Term Age: newborn, 3–4 months	Methamphetamine/ tobacco- and tobacco-exposed females had lower FA in the anterior corona radiata than control females. Methamphetamine/ tobacco-exposed males had smaller FA and larger diffusivities in the superior and posterior corona radiata, with normalization by 3 months. Tobacco-exposed infants showed persistently lower axial diffusion in the thalamus and internal capsule. Methamphetamine/ tobacco-exposed infants showed delayed developmental trajectories on active muscle tone and total neurologic scores, which normalized by 3–4 months.
Warton et al. (2018a) Drakenstein Child Health Study, Univ. of cape town	18/21 Polysubstance exposure not excluded Methamphetamine exposure quantified as 2 + uses per month	1–4 weeks postnatal* *Infants born prior to 34 weeks scanned at 7–9 weeks postnatal	T1-weighted brain volumes Regional volumes	Caudate, putamen, thalamus, hippocampus, vermis, cerebellum	N/A	Exposed infants had reduced bilateral caudate and thalamic volumes. Analyses controlled for cannabis and tobacco use.
Warton et al. (2018b) Drakenstein Child Health Study, Univ. of Cape Town	11/12 Polysubstance exposure not excluded Methamphetamine exposure quantified as 2 + uses per month	1–5 weeks postnatal (no correction for prematurity)	DTI Probabilistic tractography FA, AD, RD	OFC, caudate, nucleus accumbens, putamen, hippocampus, midbrain, amygdala	N/A	Higher exposure was associated with lower FA in connections between the striatum and midbrain, orbitofrontal cortex, and associated limbic structures. Analyses controlled for cannabis and tobacco use.
Warton et al. (2020) Drakenstein Health Study, Univ. of Cape Town	11/12 Polysubstance exposure not excluded Methamphetamine exposure quantified as 2 + uses per month	1–5 weeks postnatal* *1 premature infant born at 31 weeks GA scanned at 9 weeks postnatal	DTI Probabilistic tractography FA, AD, RD	Association fibers, projection fibers, commissural fibers	N/A	Higher exposure was associated with lower FA in bilateral association and projection and commissural networks (corticospinal tracts, internal capsule, optic radiations, thalamic radiations, uncinate, occipitofrontal fasciculus, superior and inferior longitudinal fasciculi). Higher exposure was associated with lower AD in the right association and increased RD in the right projection and bilateral association networks. Analyses controlled for cannabis and tobacco use.

Study cohorts are listed to illustrate cohort overlap across studies. Gestational age (GA) is included where reported. The Amiel-Tison Neurological Assessment at Term is a method to determine risk of neurologic injury in neonates (Gosselin et al., 2005). AD, axial diffusivity; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity. N/A = not applicable.

TABLE 4 Cocaine exposure: summary of main findings of the included studies (n = 2), including MRI and developmental outcomes.

Reference and cohort	Sample n exposed/ control	Sample age at imaging	MRI technique and parameters	Brain regions	Developmental outcome and age at testing	Main reported outcomes
Cocaine						
Grewen et al. (2014) Univ. of North Carolina at Chapel Hill	73*/46 *N = 33 exposed to cocaine with or without additional substances *N = 40 exposed to nicotine, alcohol, opiates, and/or selective serotonin reuptake inhibitors without cocaine exposure Substance exposure quantified by self-report	Mean age 5 weeks postnatal (infants born < 36 weeks excluded)	Dual contrast MRI (T1w, T2w) Regional volumes	Cortical regions: right/left dorsal, ventral, prefrontal, frontal, parietal, occipital	N/A	Infants with prenatal cocaine exposure had lower total gray matter and regional gray volume in prefrontal and frontal regions relative to controls and infants with non-cocaine drug exposure. Infants with prenatal cocaine exposure had greater total CSF volume and regional CSF volumes in prefrontal, frontal, and parietal relative to controls and infants with non-cocaine drug exposure. Analyses controlled for non-cocaine substance exposures.
Salzwedel et al. (2016) Univ. of north Carolina at chapel hill	88*/64 * N = 45 exposed to cocaine with or without other exposures. *N = 43 others exposed to non-cocaine substances. Substance exposure quantified by self-report	2–6 weeks postnatal (infants born < 32 weeks or > 42 weeks excluded)	Resting-state fMRI Functional connectivity	Thalamus and cortical regions	Bayley Scales of Infant and Toddler Development Age: 3 months	Cocaine-exposed infants exhibited hyper-connectivity between the thalamus and frontal regions and hypo-connectivity between the thalamus and motor-related regions. Thalamo-frontal connectivity in cocaine exposed infants was related to lower cognitive and fine motor skills and thalamo-motor connectivity showed a positive relationship with composite motor skills. Cocaine by selective-serotonin-reuptake-inhibitor interactions were detected.

Study cohorts are listed to illustrate cohort overlap across studies. Gestational age (GA) is included where reported. The Bayley Scales of Infant and Toddler Development is a validated scoring system to assess cognitive, language, and motor development (Bayley, 2005). N/A = not applicable.

TABLE 5 Nicotine exposure: summary of main findings of the included studies (n = 2), including MRI and developmental outcomes.

Reference and cohort	Sample n exposed / control	Sample age at imaging	MRI technique & parameters	Brain regions	Developmental outcome and age at testing	Main reported outcomes
Nicotine (tobacco smoking)						
Ekblad et al. (2010) IMAC-MIND Consortium, Germany	43/190 Alcohol exposure not excluded Nicotine exposure quantified by self-report	Imaging at term of infants born <32 weeks gestation or <37 weeks gestation with birth weight <1,500 g	T1-weighted gray matter volumes Regional volumes	Cerebral, cerebellar, frontal lobe, medulla, pons, basal ganglia, and thalami	N/A	Exposed infants had smaller frontal and cerebellar volumes than control infants. Analyses controlled for alcohol use.
MahabeE-Gittens et al. (2023) Cincinnati infant neurodevelopment early prediction study, Univ. of Cincinnati	50/345 Polysubstance exposure not excluded Nicotine exposure quantified by self-report	Imaging at 39–44 weeks post-conception of infants born at <32 weeks gestation	Regional volumes, global brain abnormality score, global efficiency of structural connectome	White matter, cortical gray matter, deep gray matter, cerebellum	N/A	Exposed infants had higher median Global Brain Abnormality Score and diffuse white matter abnormality volume than control infants. Exposed infants also had lower global efficiency and total brain tissue volume. Preterm birth mediated 0–29% of the effect of prenatal tobacco smoke exposure on brain abnormality outcomes. Analyses controlled for opioid and cannabis use.

Study cohorts are listed to illustrate cohort overlap across studies. Gestational age (GA) is included where reported. The Global Brain Abnormality Score accounts for white matter, cortical gray matter, deep gray matter, and cerebellar regions based on an MRI scoring system ([Kidokoro et al., 2013](#)). NA = not applicable.

TABLE 6 Cannabis exposure: summary of main findings of the included studies (n = 1), including MRI and developmental outcomes.

Reference and cohort	Sample n exposed/ control	Sample age at imaging	MRI technique and parameters	Brain regions	Developmental outcome and age at testing	Main reported outcomes
Cannabis						
Grewen et al. (2015) Univ. of North Caroline at Chapel Hill	43*/23 *N = 20 exposed to cannabis with or without additional substances *N = 23 exposed to nicotine, alcohol, opiates, and/or selective serotonin reuptake inhibitors without cannabis exposure Cannabis exposure quantified using self-report	2–6 weeks postnatal (infants born < 36 weeks excluded)	Resting-state functional connectivity Seed-based functional connectivity analysis	Subcortical seed regions with high fetal CB1R expression (amygdala, hippocampus, putamen, anterior/posterior insula, caudate, and anterior/posterior thalamus)	N/A	Cannabis-exposed infants demonstrated hypoconnectivity in the insula, anterior insula-cerebellum, right caudate-cerebellum, right caudate-right fusiform gyrus/inferior occipital, left caudate-cerebellum circuits. Both exposed groups (cannabis exposed and non-cannabis exposed) had hyper-connectivity of the left amygdala seed with the orbital frontal cortex and hypo-connectivity of the posterior thalamus seed with the hippocampus.

Study cohorts are listed to illustrate cohort overlap across studies. Gestational age (GA) is included where reported. N/A = not applicable.

TABLE 7 Polysubstance exposure: summary of main findings of the included studies (n = 2), including MRI and developmental outcomes.

Reference and cohort	Sample n exposed / control	Sample age at imaging	MRI technique and parameters	Brain regions	Developmental outcome and age at testing	Main reported outcomes
Polysubstance exposure						
Salzwedel et al. (2015) Univ. of North Carolina at Chapel Hill	73*/46 *N = 33 exposed to cocaine with or without additional substances *N = 40 exposed to nicotine, alcohol, opiates, and/or selective serotonin reuptake inhibitors without cocaine exposure Substance exposure quantified by self-report	Within ~4 weeks postnatal	Resting-state functional connectivity Seed-based whole-brain functional connectivity analysis	Functional connectivity between seed regions (amygdala and insula) and frontal and sensorimotor cortices	N/A	Exposed infants had connectivity disruptions in the amygdala-frontal, insula-frontal, and insula-sensorimotor circuits. A cocaine-specific effect was seen within a subregion of the amygdala-frontal network.
Salzwedel et al. (2020) Univ. of North Carolina at Chapel Hill	75/58 *N = 75 exposed to cocaine, cannabis, alcohol, nicotine, selective serotonin reuptake inhibitors, and/or opioids Cannabis exposure quantified by self-report	2–6 weeks postnatal (no correction for prematurity)	Resting-state functional connectivity Intersubject variability in functional connectivity between seed regions	Whole-brain analysis with 222 seed regions	Bayley Scales of Infant and Toddler Development Age: 3 months	~5% of whole-brain functional connections were affected by substance exposure, particularly within higher-order brain networks. Substance-specific effects included associations between nicotine exposure and bilateral medial and right lateral prefrontal regions, cocaine exposure and bilateral cingulate and left middle frontal areas, opioid exposure and right angular and left middle frontal gyrus connectivity. Regions showing significant drug effects were significantly correlated with poorer behavioral outcome measures, with a mediation role of the brain functional connectivity between exposure status and cognitive/language outcomes.

Study cohorts are listed to illustrate cohort overlap across studies. Gestational age (GA) is included where reported. The Bayley Scales of Infant and Toddler Development is a validated scoring system to assess cognitive, language, and motor development (Bayley, 2005). N/A = not applicable.

and cortex are particularly affected. Notably, volume normalization in regions such as the thalamus, caudate, putamen, and corpus callosum was observed in alcohol-exposed infants treated postnatally with choline, suggesting potential for early intervention (Warton et al., 2021). Infancy represents a critical period of rapid brain growth, particularly in white and gray matter, and slower growth during this stage has been associated with poorer developmental outcomes, suggesting that the observed structural differences may have long-term implications for substance-exposed infants (Lind et al., 2011; Peterson et al., 2003). Most studies utilized regional and global volumetric quantification approaches. However, none employed advanced quantitative MRI techniques, such as relaxometry, magnetization transfer imaging, magnetic resonance spectroscopy, or quantitative susceptibility mapping. These techniques are capable of capturing subtle developmental differences and are highly sensitive to tissue composition, including water content, myelination, and iron (Nossin-Manor et al., 2013; Sled and Nossin-Manor, 2013). The absence of these modalities limits our ability to characterize the biological underpinnings of the observed volumetric changes and offers opportunities for future studies.

rsfMRI

During infancy, brain circuits exhibit differing patterns of functional connectivity changes that generally follow a pattern of higher overall functional connectivity, higher within-network connectivity, and few aberrant connections between distinct networks (Hoff et al., 2013). The resting-state fMRI studies included in this review suggest that prenatal substance exposure to alcohol, opioids, cocaine, and cannabis is associated with widespread alterations in functional connectivity, particularly in cortical–subcortical networks. Findings support a pattern of altered development of functional connectivity in exposed infants, with aberrantly strong subcortical–cortical connections and less coherence within sensorimotor (alcohol and cocaine, Donald et al., 2016; Salzwedel et al., 2016), limbic (alcohol, opioids, cocaine, and cannabis, Grewen et al., 2015; Jiang et al., 2022; Liu et al., 2022; Radhakrishnan et al., 2021; Roos et al., 2021; Salzwedel et al., 2016) and cerebellar (cannabis, Grewen et al., 2015) networks. Interestingly, fronto-limbic changes appear attenuated in infants exposed to MOUD compared to those exposed to non-MOUD opioids, although disruptions in certain limbic-subcortical pathways persist (Liu et al., 2022). Similar patterns of altered functional connectivity have been observed in older children and adolescents with prenatal substance exposure, where they have been linked to poorer executive function and general developmental outcomes (Sirnes et al., 2018; Smith et al., 2016; Vishnubhotla et al., 2024). These early life connectivity disruptions may reflect neural circuit alterations that contribute to later behavioral and cognitive challenges seen in this population, but longitudinal research is needed to determine how early connectivity differences evolve over time and whether they can reliably predict later outcomes.

DTI

It is well established that increasing FA and decreasing diffusivity reflect key microstructural processes occurring during early brain development, such as increased axonal density, more complex fiber organization, and ongoing myelination (Friedrich et al., 2020; Song et al., 2002). DTI parameters are therefore considered sensitive markers of tissue microstructure and have been linked to favorable

developmental outcomes (Cancelliere et al., 2013; Lebel and Deoni, 2018; Qiu et al., 2008). DTI findings reviewed here suggest that prenatal substance exposure is associated with broad alterations of brain microstructure and affect a range of developing white matter tracts, including the corpus callosum, corona radiata, superior and inferior longitudinal fasciculi, and internal and external capsules. Lower FA in major white matter tracts may represent less myelination and/or reduced organization (Lebel and Deoni, 2018). Moreover, studies reporting higher RD and lower AD across white matter tract supports the hypothesis of reduced myelination and altered fiber organization in substance-exposed infants (Harsan et al., 2006; Song et al., 2002). Patterns of white matter MD differences between exposed and control groups were less consistent across studies, with most studies reporting increased MD and (Taylor et al., 2015) reporting decreased MD in white matter tracts in exposed infants. This variability may reflect regional and substance-specific differences in the impact of prenatal substance exposure across the brain, where effects do not necessarily occur uniformly or in the same direction across all white matter regions. Additionally, since RD and AD both contribute to the calculation of MD, different relationships between prenatal substance exposures and RD or AD may also contribute to the opposite directionality of the effect on MD across substances and regions (Counsell et al., 2006; Lebel et al., 2019; Winklewski et al., 2018). Further, existing literature has reported patterns of more developed white matter (higher FA and lower MD) of fronto-limbic regions in socioeconomically disadvantaged infants (Lean et al., 2022), suggesting an adaptation to environmental stress. The higher maturity observed in fronto-limbic regions has not been documented in substance exposure, but it may explain the deviations from the generally observed decrease in white matter maturity in substance-exposed infants. Importantly, the diffusion imaging studies reviewed here relied solely on conventional DTI modeling. More advanced techniques such as diffusion kurtosis imaging (DKI) and neurite orientation dispersion and density imaging (NODDI), among others, may offer additional sensitivity and specificity to underlying neurobiological alterations (DiPiero et al., 2023; Steven et al., 2014; Zhang et al., 2012). However, these approaches are limited by longer acquisition times and higher b-values, which may reduce feasibility in neonatal populations (DiPiero et al., 2023).

The neuroimaging associations observed in substance-exposed infants are likely driven by multiple complex and interacting biological mechanisms. Prenatal substance use may disrupt maternal systemic and placental physiology, potentially limiting the availability of critical nutrients required for healthy brain development (Ross et al., 2015). These disruptions may underlie the reductions in gray and white matter volumes, compromised microstructural integrity, and altered resting-state functional connectivity observed in exposed infants (Eléfant et al., 2020; Rees and Harding, 2004). Additionally, prior research in adolescents has identified structural and functional brain differences, such as increased neural activation, reduced brain volumes, and diminished white matter integrity in regions involved in reward processing and reinforcement (De Genna et al., 2022; Ernst et al., 2001; Sirnes et al., 2018; Vishnubhotla et al., 2024). These neurodevelopmental changes are associated with a heightened risk for substance use behaviors; therefore, similar early-life imaging signatures in substance-exposed infants represent neurobiological vulnerabilities that may predispose individuals to substance use disorders later in life (Abu and Roy, 2021; Nygaard et al., 2017; Oei, 2018; Squeglia and Gray, 2016).

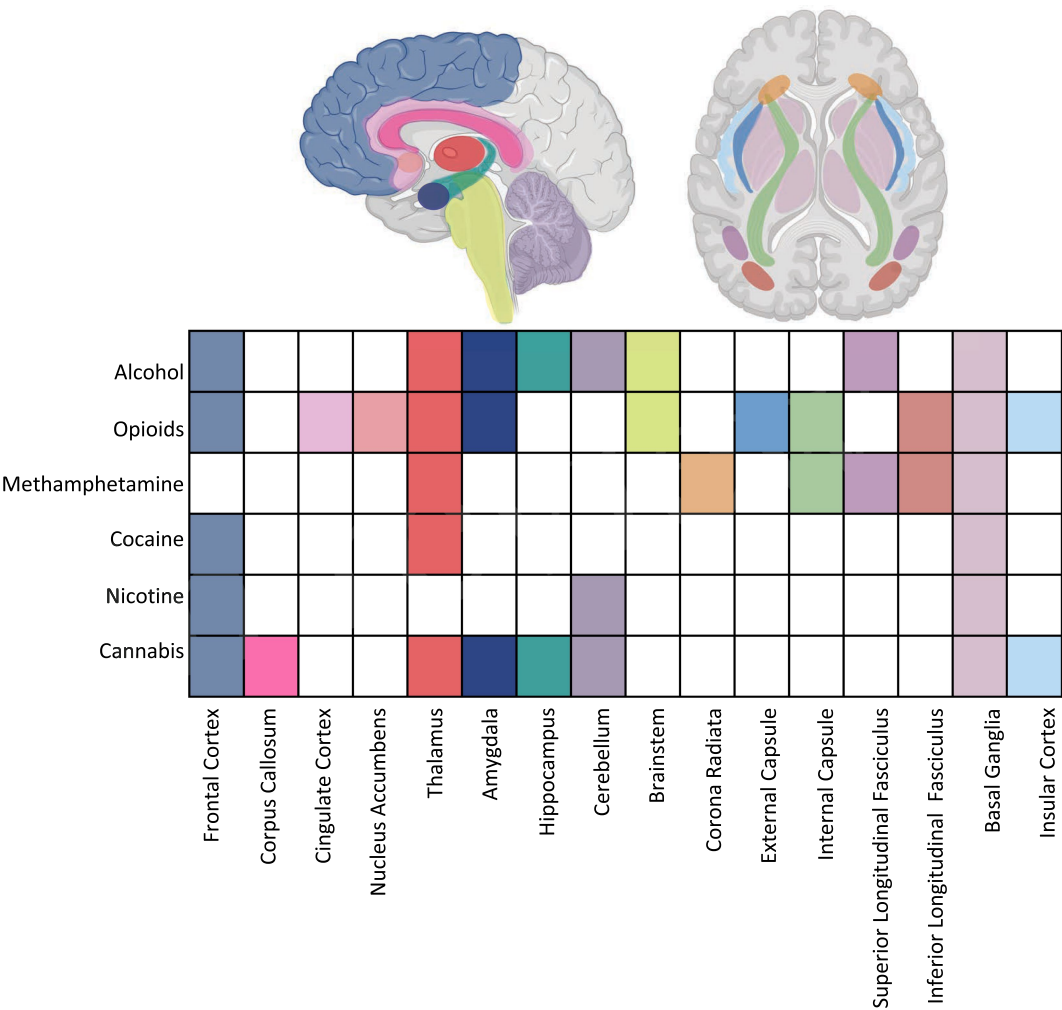


FIGURE 1
Summary of imaging findings across substance exposures highlighting target regions. Created in <https://BioRender.com>.

Brain regions and circuits of interest

Evidence from the included studies suggests both overlapping and distinct patterns of brain alterations associated with prenatal exposure to different substances. Several regions appear consistently vulnerable across substances, while others show exposure-specific associations (Figure 1).

Across substances, including opioids, alcohol, methamphetamine, cannabis, and polysubstance use, exposed infants consistently exhibit alterations in structures within the reward and limbic systems, including the amygdala, nucleus accumbens, hippocampus, basal ganglia, and insula that are associated with these exposures. Given the widespread effects of prenatal substance exposures on these regions, reward and limbic differences may represent a shared neural phenotype of prenatal substance exposure. The involvement of these networks in infants exposed to substances parallels alterations within the reward system reported among adolescents with substance use disorders (Salmanzadeh et al., 2020; Squeglia and Gray, 2016). Early disruptions in these circuits may compromise affective processing and reward sensitivity, possibly mediated by perturbations in dopamine signaling due to substance exposure (Sesack and Grace, 2010).

Ultimately, reward circuitry changes evident in infancy could contribute to heightened vulnerability for later-life substance use (Dodge et al., 2019), although this risk likely emerges from a complex interplay of genetic predisposition, neurobiological consequences of exposure, and broader environmental and social determinants (Abu and Roy, 2021; Nygaard et al., 2017; Oei, 2018).

Further, differences in primary sensory and motor relay centers, such as the thalamus, internal and external capsules, and corticospinal tract, were reported in infants with prenatal exposure to opioids, alcohol, and methamphetamine. These findings are consistent with adult studies linking substance use with alterations in similar relay structures (Huang et al., 2018; Pando-Naude et al., 2021) and suggest a vulnerability of sensorimotor pathways, potentially driven by disruptions in excitatory and inhibitory (glutamate and GABAergic) signaling which are affected across substance exposures and are critical to early thalamocortical and corticospinal development (Luján et al., 2005; Nishimaru and Kakizaki, 2009; Amitai, 2001). Given the role of these tracts in motor coordination and sensorimotor integration, disruptions may underlie the motor impairments observed in substance-exposed infants and children (Salzwedel et al., 2016; Willford et al., 2010).

Additionally, cortical disruptions, particularly within the frontal and prefrontal cortex were observed in infants exposed to opioids, cocaine, cannabis, nicotine, or polysubstance use (Ekblad et al., 2010; Grewen et al., 2014, 2015; Radhakrishnan et al., 2021; Salzwedel et al., 2020; Salzwedel et al., 2015, 2016). These regions, particularly within the prefrontal cortex, have frequently been implicated in adults and adolescents with substance use disorders and have been associated with cognitive and executive function impairments (Goldstein and Volkow, 2011; Squeglia et al., 2009). Dysfunction in these regions may contribute to the cognitive findings observed in infancy (Donald et al., 2015b; Salzwedel et al., 2020; Salzwedel et al., 2016). This may be driven by disruptions to synaptic pruning, myelination, or neurochemical systems such as dopamine and GABA, which shape early cortical development (Ojeda and Ávila, 2019).

Substance-specific patterns also emerged. For example, cerebellar differences were most consistently reported in infants exposed to alcohol, nicotine, and cannabis, suggesting selective vulnerability of cerebellar networks to these substances. This substance-specific pattern may be related to the high concentration of GABA (target for alcohol), cholinergic and nicotinic (targets for nicotine), and cannabinoid (target for cannabis) receptors in the cerebellum (Hauser et al., 2003; Hsiao et al., 1999; Takahashi and Linden, 2000), although future work in large samples is needed to further assess the effects of additional substance exposures on cerebellar development. Given the cerebellum's role in sensorimotor coordination and emerging links to cognitive function, its alteration may underlie both motor and attentional deficits observed in exposed populations (Konczak and Timmann, 2007; Lyu et al., 2025).

While not the primary focus of this review, regions implicated in human infant neuroimaging studies are well-supported by preclinical literature on prenatal substance exposure (Ross et al., 2015). Animal studies have found that prenatal stimulants may affect dopaminergic system development (Thompson et al., 2009), while prenatal cocaine exposure may alter basal ganglia, hippocampus, amygdala, and cortical development (Dow-Edwards et al., 1990). Alcohol exposure in utero has been linked to abnormalities in the neocortex, hippocampus, cerebellum, and other regions (Guerri, 2002). Additionally, murine models have implicated the hippocampus and basal ganglia (opioids), hippocampus and cortex (nicotine), and the cerebellum, thalamus, hypothalamus, and hippocampus (cannabis) in substance-related developmental disruption (Benevenuto et al., 2022; Byrnes and Vassoler, 2018; Roy et al., 2002). This overlap between human neuroimaging and preclinical data provides a valuable foundation for future mechanistic studies.

In sum, the current literature suggests a core set of regions, including the limbic and reward systems, white matter relay tracts, and the frontal cortex, that are commonly affected across exposure types, possibly reflecting shared neurodevelopmental mechanisms (e.g., dysregulation of dopamine, glutamate, and GABA systems). At the same time, certain regions such as the cerebellum appear to show more substance-specific vulnerability, underscoring the importance of both common and unique pathways through which prenatal exposures impact early brain development. Nonetheless, results are preliminary, within small samples with significant cohort overlap between studies, so additional substance-specific effects and effects across substance exposures may be revealed with future work. Implicated regions aligned with both adolescent studies and animal models of prenatal substance exposure. Further whole-brain analyses

examining effects of prenatal substance exposure may reveal additional relationships across the brain.

Developmental consequences of prenatal substance exposure

Prenatal substance exposure has been linked to a range of developmental outcomes in infancy, but the existing neuroimaging literature provides limited insight into the neurobiological mechanisms of these associations. Across alcohol and methamphetamine exposures, neuroimaging findings were associated with impairments in central and peripheral neurological function in the neonatal period. In substance exposed infants, neuroimaging differences relative to healthy controls were associated with poorer cognitive and fine motor skills (cocaine exposure) and worse cognitive and language skills (polysubstance exposure) on the BSID-III at 3 months of age. These associations provide early insight into how substance-related alterations in brain structure and function may translate into long-term developmental challenges. Nonetheless, while a number of included studies reported abnormal developmental findings at birth in substance exposed infants, one study reported normalization of these findings by 3–4 months of age, highlighting the need for longitudinal follow-up of developmental findings (Chang et al., 2016). Moreover, by design, few included studies evaluated development beyond the neonatal period, making it challenging to contextualize the long-term functional relevance of neuroimaging findings.

Thus, it remains unclear whether these outcomes reflect a delay in developmental progression, permanent deficits in specific neural systems, or a combination of both mechanisms. Such ambiguity underscores the need for longitudinal studies to track developmental trajectories over time in exposed infants. Importantly, protective factors, including supportive caregiving, parental mental health, and enriched home environments, have been shown to moderate adverse outcomes in adolescence and may serve as critical buffers against early brain vulnerability (Bada et al., 2012; Motz et al., 2011). Future neuroimaging studies should examine how these protective factors influence the relationship between prenatal substance exposure and brain development.

Clinical intervention studies

While not the main focus of this work, two studies explored the impact of medications for substance use. One study found normalized regional brain volumes in the thalamus, basal ganglia, and corpus callosum in pregnant people with alcohol exposure treated with high-dose choline supplementation during pregnancy, which related to better recognition memory at 12 months, compared with non-treated alcohol exposed infants (Warton et al., 2021). Another study found a reduction in opioid-associated changes in rsFC in infants exposed to methadone therapy relative to infants exposed to opioids without treatment (Liu et al., 2022; Radhakrishnan et al., 2021). These studies provide promising evidence for treatment-related effects on infant brain development, albeit in small sample sizes. Future work should continue to evaluate treatment-related effects of medications for substance use in pregnancy on infant brain and developmental outcomes.

Limitations in the current literature

One overarching limitation is the small sample sizes across studies, with exposed infant cohorts ranging from 10 to 88 participants. Additionally, most studies excluded occasional users but did not consistently address critical variables such as dosage or timing of substance exposure which are likely to influence outcomes and clinical translation of findings. A tightly orchestrated sequence of neurodevelopmental events unfolds throughout gestation, with varied developmental trajectories across brain circuits and regions, so the timing of substance exposures across trimesters may have varying impacts on brain development and merits further examination with sufficiently powered analyses (Andescavage et al., 2017; Xu et al., 2022). Only 2 studies within the same cohort (Warton et al., 2020; Warton et al., 2018b) examined dose effects, and none evaluated timing of exposure. Polysubstance use presents an additional methodological challenge. Although some studies focused on or included data from polysubstance-exposed groups, most did not control for the influence of multiple exposures. Therefore, observed neural differences may reflect synergistic effects or confounding interactions between commonly co-ingested substances such as alcohol, nicotine, and cannabis. Furthermore, although some studies linked neuroimaging signatures to developmental outcomes, these associations were typically based on cross-sectional assessments conducted at the time of imaging. Few studies explored infant developmental outcomes beyond the first weeks of life. No included studies assessed whether imaging findings were associated with clinical diagnoses, such as FASD or NWS, which could help contextualize these neuroimaging findings. Similarly, no studies included comparisons between neuroimaging findings and physiological measures such as inflammatory markers or hormonal changes, which are known to be disrupted in fetal substance exposure (Frank et al., 2011; Franks et al., 2019; Salisbury et al., 2009).

Further, the existing body of literature is limited in its control of confounding factors and co-occurring influences that could contribute to observed differences between substance-exposed infants and healthy control infants. These factors include maternal psychosocial health, use of prescription medications, physical health status, and socioeconomic conditions, which may independently impact fetal brain development and interact with substance exposure (Mravčík et al., 2020). Although studies variably excluded or controlled for preterm birth, prematurity itself is linked to altered neurodevelopment and is more common among substance-exposed neonates (Bada et al., 2005; Ortinau and Neil, 2015; Umer et al., 2023). One study found that prematurity mediated nearly one-third of the effect of tobacco exposure on brain development, highlighting its significant influence (Mahabee-Gittens et al., 2023).

Sex differences also remain underexplored. Only one study in this review reported sex-specific findings (Chang et al., 2016), despite established sex-related differences in brain development and susceptibility to prenatal insults, including substance exposure (Dipietro and Voegtline, 2015; Hines, 2010; Kaczurkin et al., 2019; Terasaki et al., 2016). Future studies should prioritize evaluating sex-specific effects to more precisely identify vulnerable subgroups.

Finally, the predominantly cross-sectional nature of included studies limits the ability to determine whether observed neural differences represent long-term changes or delays that might resolve with early intervention. Longitudinal imaging studies will be crucial to

understanding whether and how brain alterations evolve across development. While infant neuroimaging findings mirror those reported in older children and adolescents, including disruptions in cortical, cerebellar, and fronto-limbic structures, as well as in the basal ganglia, corpus callosum, amygdala, and hippocampus, postnatal experiences and social environments continue to shape neural development over time (Derauf et al., 2009; Willford et al., 2016). These dynamic interactions emphasize the need for long-term follow-up studies.

Current review: methodological limitations

Certain limitations of this review should be noted. First, despite efforts to develop a comprehensive search strategy, including reviewing the bibliographies of the studies in this review, it is possible that some relevant studies may not have been included due to the limitations of the selected databases and search terms. Variability in how studies are indexed and the terminologies used by the authors may have contributed to the omission of pertinent literature. Additionally, to include all existing literature on imaging findings in infants with substance exposure, diffusion-weighted, structural, and functional MRI are included in this review, making direct comparisons between these studies challenging. Moreover, since the initial database search was conducted by a single author, this may introduce a limitation regarding potential selection bias.

Within modalities, different statistical approaches and techniques for delineating regions of interest were applied. For example, among the DTI analyses, tract-based spatial statistics were leveraged in two studies; four studies utilized probabilistic tractography to delineate regions of interest and one study used atlas-segmented regions of interest. Similarly, brain volumes could not be directly compared across the existing structural data, which applied T1-/T2-weighted MRI, T1-weighted MRI, T2-weighted MRI, or proton density-weighted MRI to estimate brain volumes. These methodological inconsistencies may account for some differences observed across studies.

Additionally, several studies originated from the same research groups or used overlapping samples, potentially biasing findings. Some infants were scanned beyond the neonatal window, introducing postnatal environmental influences that could confound results. Furthermore, the focus on infancy may limit the generalizability of findings to later developmental stages, although existing reviews in older populations complement this work (Irner, 2012; Sanjari Moghaddam et al., 2021).

Future directions

Despite these limitations, the findings of this review point to meaningful differences in brain development associated with prenatal substance exposure, particularly in the context of polysubstance use, which warrants further study given its high prevalence (Jarlenski and Krans, 2021). Future research should continue to evaluate the distinct and combined effects of individual substances on brain development while accounting for moderating variables such as sex, gestational age, birth weight, maternal mental health, and socioeconomic status (Dufford et al., 2021; Pulli et al., 2018).

Additional investigation into affected neural circuits, especially those involved in reward processing, sensory-motor integration,

cognition, and white matter connectivity, is warranted. Researchers should leverage modern diffusion-weighted models and quantitative structural techniques to further investigate affected brain regions. Longitudinal studies are especially needed to clarify how early neural alterations relate to evolving developmental trajectories and functional outcomes.

Further, examining the impact of the timing and dosage of prenatal substance exposure will be critical for disentangling its specific neurodevelopmental effects. Understanding whether pharmacological or psychosocial interventions can mitigate adverse outcomes is essential to inform clinical care and public health policy. Large, diverse, and nationally representative samples will be necessary to contextualize substance-related effects within broader social and environmental risk factors.

Conclusion

Evidence from structural, functional, and diffusion MRI data suggests that prenatal substance exposure is associated with measurable alterations in infant brain development. These effects vary by substance type, co-exposures, and affected brain regions, and are associated with early developmental outcomes. However, small sample sizes and imprecise exposure measurement limit the strength of current conclusions. Failure to account for additional sources of disadvantage, sex, and prematurity also limits current work. Continued large-scale, longitudinal research is needed to refine our understanding of how prenatal exposures impact brain development, inform clinical practice, and guide supportive policies for affected families.

Author contributions

LS: Writing – review & editing, Conceptualization, Investigation, Writing – original draft, Visualization, Methodology, Formal analysis. CY: Methodology, Writing – review & editing, Visualization. AL: Writing – review & editing, Visualization. LS: Data curation, Writing – review & editing, Visualization. ER: Writing – review & editing, Data curation, Visualization. EP: Supervision, Methodology, Writing – review & editing, Conceptualization. DD: Writing – review & editing, Methodology, Conceptualization, Supervision.

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Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the National Institutes on Drug Abuse (R34 DA050258). LS was partially supported by T32 GM140935. DD was supported by R00 MH11056 and EP was supported by K01 MH113710 from the National Institute of Mental Health. CY was supported by T32HD007489. DD was supported by U54 HD090256. Infrastructure support was also provided, in part, by grant P50 HD105353 (Waisman Center). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Acknowledgments

We would like to acknowledge Andrew Alexander for supporting this work.

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