Drug and Alcohol Dependence 198 (2019) 39–53

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Review

Prenatal drug exposure from infancy through emerging adulthood: Results from neuroimaging

Kristen P. Morie[a,b,*], Michael J. Crowley[a,b], Linda C. Mayes[b,c,d], Marc N. Potenza[a,b,e,f,g]

[a] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, 06510, USA
[b] Child Study Center, Yale University School of Medicine, New Haven, CT, 06510, USA
[c] Department of Pediatrics, Yale University School of Medicine, New Haven, CT, 06510, USA
[d] Department of Psychology, Yale University, New Haven, CT, 06511, USA
[e] Department of Neuroscience, Yale University School of Medicine, New Haven, CT, 06510, USA
[f] Connecticut Mental Health Center, New Haven, CT, 06519, USA
[g] Connecticut Council on Problem Gambling, Wethersfield, CT, 06109, USA

ARTICLE INFO

Keywords:
Prenatal exposure
Drugs of abuse
Cognitive control
Reward processing
Development
Neuroimaging

ABSTRACT

Prenatal drug exposure may have important repercussions across the lifespan for cognition and behavior. While alcohol is a recognized teratogen, the influences of other substances may also be substantial. The neural underpinnings of the influences of prenatal drug exposure have been examined using longitudinal approaches and multiple imaging techniques. Here we review the existing literature on the neural correlates of prenatal drug exposure. We focused the review on studies that have employed functional neuroimaging and electroencephalography and on substances other than alcohol. We also framed the review through the lens of four developmental life stages (infancy, childhood, adolescence and emerging adulthood). We included papers that have examined any drug use, including tobacco, opiates, cocaine, marijuana, methamphetamines, or polysubstance use. Data suggest that prenatal drug exposure has long-lasting, deleterious influences on cognition and reward processing in infancy and childhood that persist into adolescence and emerging adulthood and may underlie some behavioral tendencies, such as increased externalizing and risk-taking behaviors, seen in these groups.

1. Introduction

Drug use by pregnant women is a major public health concern. Exposure to drugs of abuse prenatally has been linked to increased risk-taking behaviors, more impulsivity and increased incidence of conduct disorder (Fisher et al., 2011), and notably, increased likelihoods of substance-use initiation (Delaney-Black et al., 2011; Richardson et al., 2013). Prenatal exposure may begin a pattern of disadvantages that persists throughout an individual's life and potentially into the following generation. As individuals move from childhood through adolescence into emerging adulthood, neural processes may interact with environmental factors to lead to impairments in day-to-day functioning, with possible consequences for functioning into adulthood. The goal of this review is to examine the potential influences of prenatal drug exposure, including marijuana, nicotine, cocaine, methamphetamine, and opiates, on brain function. Previous reviews have examined the effect of prenatal exposure on brain development and behavior and its implications on policy (Thompson et al., 2009). Behavior in early childhood as a consequence of prenatal substance exposure has also been reviewed (Frank et al., 2001). Influences of prenatal substance exposure with respect to functional neuroimaging have been reviewed in childhood (Derauf et al., 2009), with a focus on individual substances, including alcohol. This review extends prior ones by including findings that have been published in the past ten years, focusing on substances other than alcohol (although alcohol may be included as a drug in instances of polysubstance abuse), and providing a developmental perspective, considering several major life stages, including infancy/childhood, adolescence, and emerging/young adulthood, in order to document the impacts of prenatal exposure on brain function and behavior in these developmental epochs. We focus on studies that have employed functional neuroimaging methods to examine brain function in humans, including functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG), as well as methodologies that offer insight into connectivity, including diffusion tensor imaging (DTI) and resting-connectivity measures. EEG/ERP and MEG help delineate temporal aspects of neural

* Corresponding author at: Department of Psychiatry, Yale University School of Medicine, 300 George St., #901, New Haven, CT, 06510, USA.
E-mail address: kristen.morie@yale.edu (K.P. Morie).

https://doi.org/10.1016/j.drugalcdep.2019.01.032
Received 13 July 2018; Received in revised form 15 January 2019; Accepted 15 January 2019
Available online 28 February 2019
0376-8716/

Table 1
Infancy.

Citation	Title	Exposure Type	Technique	Participants	Main Finding
Salzwedel et al., 2015	Prenatal drug exposure affects neonatal brain functional connectivity.	Polysubstance	Resting state functional connectivity	45 PCE, 43, polysubstance-exposed w/o cocaine, 64 exposure-free, 305-308 days gestational age	Drug exposure-related connectivity disruptions were found between amygdala-frontal, insula-frontal, and insula-sensorimotor circuits. A cocaine-specific effect was found in the amygdala-frontal network. Functional connectivity alterations showed a left-lateralized pattern
Hansen et al., 1993	Visual evoked potentials and visual processing in stimulant drug-exposed infants.	Cocaine and/or amphetamines	ERP-Visual Evoked Potentials	8 PCE and/or amphetamines, 8 exposure-free, 37-41 weeks of age	Exposed infants showed worse performance on a visual recognition test, but no differences on VEP testing.
Whitham et al., 2010	The effects of prenatal exposure to buprenorphine or methadone on infant visual evoked potentials.	Opiates	ERP-Visual Evoked Potentials	22 ME, 30 PBE, 33 Non-opioid exposed, 4 months of age	Methadone-exposed infants had prolonged VEP latencies compared to controls and to buprenorphine exposed infants.
Paul et al., 2014	Development of auditory event-related potentials in infants prenatally exposed to methadone.	Opiates	P2 auditory ERP	60 PME, 4-15, 16-32, or 33-120 days post-natal age	Older groups showed increased P2 amplitudes at frontal areas and increased change detection performance indicated by P2. These patterns were not seen in younger groups.
Salzwedel et al., 2016	Thalamocortical functional connectivity and behavioral disruptions in neonates with prenatal cocaine exposure	Cocaine	Resting state functional magnetic resonance imaging	45 PCE, 43 polysubstance-exposed w/o cocaine, 64 NDE, 2-6 weeks of age	PCE infants showed evidence of hyper-connectivity between thalamus and frontal regions and hypo-connectivity between thalamus and motor-related regions. Thalamo-frontal connectivity was inversely related to cognitive and fine motor scores and thalamo-motor connectivity was positively related to motor control scores.
Walhovd et al., 2012	Neural tract development of infants born to methadone-maintained mothers.	Opiates	Diffusion weighted imaging	13 ME, 7 NDE, 13-44 days of age	Methadone-exposed infants showed higher mean diffusivity in the superior longitudinal fasciculus compared to control participants.
Grewen et al., 2015	Functional connectivity disruption in neonates with prenatal marijuana exposure	Marijuana	Resting state functional connectivity	20 prenatal MJ-exposed with other exposures, 23 Non-prenatal MJ exposed with other exposures, 20 exposure-free, 2-6 weeks of age	Marijuana-exposed infants showed evidence of hypo-connectivity in the insula, and in connections in anterior insula–cerebellum networks, right caudate–cerebellum networks, right caudate–right fusiform gyrus/inferior occipital networks, and left caudate–cerebellum networks.
Scher et al., 2000	Effects of prenatal cocaine/crack and other drug exposure on electronencephalographic sleep studies at birth and one year	Cocaine/Crack primarily, polysubstance	EEG	37 PCE infants with other exposures, 34 NCE (some prenatal tobacco and alcohol exposure), 2nd day of life and 1 year of age	PCE infants showed poorer spectral correlations at birth, and lower spectral power in low-frequency bands at 1 year. Alcohol, marijuana and tobacco were associated with increased time awake.
Scher et al., 1998	Effects of prenatal substance exposure: altered maturation of visual evoked potentials	Polysubstance	ERP-Visual Evoked Potentials	74 prenatally exposed children at 4, 8, 18 months, exposure at different trimesters recorded	Exposure to substances, including alcohol, resulted in alterations of VEP latency and amplitude at different timepoints within infancy. The general pattern was of prolonged latencies, suggesting a delay in maturation of the visual system.
Chang et al., 2016	Sex-Specific Alterations of White Matter Developmental Trajectories in Infants with Prenatal exposure to methamphetamine and tobacco	Methamphetamine, Tobacco	Diffusion weighted imaging	36 PME/PTE, 32 PTE, 71 NDE controls, 1 week-4 months of age	ME/tobacco-exposed boys showed lower FA in superior and posterior corona radiata at 1week-2 months, but these differences were not seen at 3 months. ME/Tobacco exposed girls showed lower FA in anterior corona radiata at all time points. Tobacco-exposed infants of both genders showed less diffusion in the thalamus and internal capsule.

(*continued on next page*)

Table 1 (*continued*)

Citation	Title	Exposure Type	Technique	Participants	Main Finding
Wharton et al., 2018	Prenatal methamphetamine exposure is associated with corticostriatal white matter changes in neonates	Methamphetamine	Diffusion weighted imaging-tractography	11 PME newborns, 1-5 weeks, 12 non-exposed (some tobacco exposure), mean age of 2.7 weeks	ME exposed infants showed FA reductions in connections between the midbrain/left putamen, right putamen/right OFC, and right putamen/ right amygdala. Methamphetamine exposure was correlated with reduced FA in these tracts.
Kivisto et al., 2015	Somatosensory and auditory processing in opioid-exposed newborns with neonatal abstinence syndrome: a magnetoencephalographic approach	Opiates	MEG somatosensory (SEFs) and auditory evoked magnetic fields (AEFs)	11 PBE, 12 NDE, 2-30 days of age	At the group level, buprenorphine-exposed infants showed Auditory Evoked Magnetic Fields (AEFs) that were not different from those with no exposure. Four buprenorphine-exposed infants showed altered AEF morphology.

PCE = Prenatal cocaine exposure, NCE = Non-cocaine exposed, PME = prenatal methadone exposure, PTE = Prenatal Tobacco Exposure, PBE = Prenatal buprenorphine exposure, NDE = Non-drug exposed, MJ = Marijuana, VEP = visual evoked potential, AEF = Auditory Evoked Magnetic Field, EEG = Electrophysiology, ERP = event related potential, SEF = Somatosensory evoked magnetic field, P2 = P200 event-related potential.

processes and are cost-effective and easy to administer (Bell and Cuevas, 2012). A review (Neil and Smyser, 2018) discusses the strengths of different functional imaging techniques. Traditional analytic approaches such as those based on general linear models (GLMs) used to interrogate data from fMRI studies permit investigation of activity in brain regions during tasks, and resting-state functional connectivity allows for the investigation of neural networks. Diffusion MRI may be used to investigate measures related to integrity of white-matter structures. Each of these modalities has a different focus, and including all of them in a review may offer a more comprehensive understanding of cognitive processing in prenatally exposed individuals.

2. Infancy

Infancy is the life stage defined by birth to approximately 36 months of age, with rapid growth rate and rapid progression through cognitive milestones (Johnson and Blasco, 1997). Studying the influences of prenatal exposure on infants is important considering that such exposures may have already exerted impacts on neural development. Additionally, detrimental effects of prenatal exposure may be more obvious due to the recency of exposure. Perhaps due to difficulty performing experiments on infants, there are fewer studies involving infants. However, the measurement of event-related potentials (ERPs) using EEG, as well as resting connectivity and diffusion-weighted MRI techniques are non-invasive and require little or no response from participants. Thus, experiments using these techniques may provide insights into structural characteristics and neural functioning in infancy. Twelve papers have examined neural correlates of prenatal drug exposure in infancy using these techniques. Table 1 also summarizes these findings.

Three papers employed resting-state connectivity in prenatally drug-exposed infants, with results suggesting altered connectivity. In 152 neonates at 2–6 weeks of age who had been exposed *in utero* to cocaine and other substances, cocaine alone, other substances in the absence of cocaine, or no drugs, altered resting-state connectivity was found in relation to drug exposure in circuits related to arousal regulation (Salzwedel et al., 2015). Relatively increased connectivity was found in the drug-exposed groups in amgydala-frontal and insula-frontal circuits, and relatively decreased connectivity was found in insula-sensorimotor circuits. In a subsequent manuscript, the same research group reported how connectivity was associated with motor behaviors (Salzwedel et al., 2016). Once again, connectivity to frontal regions was relatively increased in drug-exposed infants, with increased connectivity observed between the thalamus and frontal regions. Conversely, connectivity was decreased between the thalamus and motor regions. Cognitive and fine motor scores were inversely correlated with thalamo-frontal connectivity and positively related to thalamo-motor connectivity. These findings are similar to those from resting-state studies of cannabis-exposed infants (Grewen et al., 2015). In infants exposed to any substance (including cannabis, nicotine, alcohol, opiates, or serotonin-reuptake inhibitors), Grewen et al. (2015) found relative hyperconnectivity between frontal regions and regions of the amydgala, and relative hypoconnectivity between regions of the thalamus and hippocampus. Unlike Salzwedel et al. (2016), there were no findings linked specifically to prenatal cocaine exposure (PCE) in the Grewen et al. (2015) sample. These findings suggest that it may be important to consider polysubstance exposure influences. In addition, cannabis-specific hypoconnectivity was observed in striatal and insula connections, including those involving the anterior insula to cerebellum, right caudate to cerebellum, right caudate to right fusiform gyrus/inferior occipital cortex, and left caudate to cerebellum. Resting-state data suggest that drug exposure has implications for connectivity between regions important for arousal and motivation in infancy. However, as polysubstance use is prevalent in mothers who use substances, it is not clear from the existing data which substances are particularly impactful with respect to connectivity between these regions.

Connectivity may also be measured, albeit indirectly, with diffusion-weighted methodologies, to examine brain white-matter tracts (Basser and Pierpaoli, 1996). White-matter values can be reported using indices of diffusivity, including fractional anisotropy (FA) and mean diffusivity (MD) (Smith et al., 2006b). Three studies using this methodology exist in infants. The first examined white matter in 13–44 day-old infants exposed to methadone (Walhovd et al., 2012). Higher MD, indicating potentially less developed white matter, was found in the superior longitudinal fasciculus, a large bundle of tracts that runs between the frontal lobe and the temporal and occipital lobes. This finding suggests possible developmental disruption by methadone exposure, although the potential impact of other drugs cannot be excluded given substance use that often occurs among individuals receiving methadone maintenance.

Tractography, an analysis method that measures connections between brain regions using a data-driven approach, has also been used to examine white matter in methamphetamine-exposed newborns, with a mean age of 2.7 weeks (Wharton et al., 2018). The authors found that in newborns, methamphetamine exposure was associated with reduced white-matter connectivity between multiple regions, including between the midbrain and putamen, the right putamen and the orbitofrontal cortex (OFC), and the right putamen and right amygdala. A second study examined white matter in methamphetamine- and tobacco-exposed newborns at three timepoints from 1 week to 4 months of age. The authors also examined the effects of gender (Chang et al., 2016). They found that while tobacco exposure was associated with less diffusion in the thalamus and internal capsule in both genders and at all time points, the combination of methamphetamine exposure and tobacco resulted in different patterns in males and females. In males, lower FA in the anterior and posterior corona radiata was found for the early time points and normalized at 3 months. However, in girls, reduced FA was found consistently in the anterior corona radiata.

Taken together, the white-matter findings suggest alterations in brain connectivity incredibly early in life, which may differ by gender. The findings have implications for development.

EEG may also be used to examine neural development during infancy. One study examined EEGs during sleep in infants with PCE (who had exposure to other substances as well), both at birth and at one year (Scher et al., 2000). EEGs collected during sleep eliminate some methodological limitations of infant research, requiring no responses, and provide insight into neural development. Infants with PCE showed poorer spectral correlations at birth (comparisons of EEG measures between pairs of EEG channels, indicating consistency between homologous brain regions). Additionally, PCE infants showed reduced amplitudes of low-frequency spectral bands (theta and beta). While the findings suggest altered development of the central nervous system (CNS), it is not clear if these differences were related to changes in functional behaviors as infants were asleep.

Evoked potentials, such as the visual-evoked potential (VEP) and auditory-evoked potential (P2), can be used as indices of the development of the visual and auditory systems, respectively (Goldie, 1992; Taylor and McCulloch, 1992). The VEP and P2 have been used to examine exposure to both cocaine and opiates in infants. To date, five studies have used EEG to examine neural processing in *in utero* drug-exposed infants. A small sample of infants (4.5 months on average) prenatally exposed to cocaine and/or amphetamine (Hansen et al., 1993) was compared to controls (n = 8 per group). No between-group differences were observed in amplitude or latency of the VEP. However, cocaine- and/or amphetamine-exposed infants performed worse on a visual recognition test conducted between 6–10 months of age. However, longer latencies of VEPs were observed in four-month-old infants exposed to methadone compared to non-exposed infants (Whitham et al., 2010). Another study examined VEPs in a cohort of infants who had been exposed to different substances, including tobacco, marijuana, illicit drugs and alcohol (Scher et al., 1998). The authors took a developmental approach, measuring VEPs at three different time points when infants were 4, 8, and 18 months old. The authors also recorded in which trimester the infants were exposed, correlating it with amplitude latency of the VEPs. Latencies of the VEPs were found to be generally longer in exposed infants, persisting even at the 18-month mark for substances like marijuana and tobacco. Amplitudes were also generally smaller with increased exposure. Taken together, the VEP data on exposed infants suggest maturational delays in the visual system.

Methadone exposure may also influence auditory processing, as indexed by the P2. In a study assessing P2 amplitude at 4–15 days, 16–32 days, or 33–120 days, differences were observed only in the older infants (Paul et al., 2014). Considering that the P2 may index healthy auditory processing in newborns, findings suggest that methadone exposure hinders auditory development. The results from Paul et al., 2014, however, should be considered with respect to limitations of the study, which had no comparison group of typically developing infants and in which the infant sample was being treated with replacement medication for neonatal abstinence syndrome. In addition, infants also had prenatal exposure to other substances, including a high prevalence of prenatal tobacco exposure.

One study used magnetoencephalography (MEG) to investigate buprenorphine-exposed infants (Kivisto et al., 2015). MEG measures similar processes as EEG, but offers slightly better spatial resolution due to less distortion of magnetic fields by the skull and scalp. Somatosensory-evoked magnetic fields (SEFs) and auditory-evoked magnetic fields (AEFs) were examined in 11 infants exposed *in utero* to buprenorphine and 12 infants without such exposure. AEFs and SEFs were similar across groups, although SEFs were disrupted in 4 of the exposed infants. As each paper employing EEG or MEG investigated exposure to a different primary substance, it is difficult to draw conclusions about the ramifications of a particular substance exposure on sensory processing in infants. However, more consistent differences have been reported in cortical connectivity in exposed infants, which could have ramifications for higher-order processing that may not be measured in infancy. In addition, there is evidence for mild impairments in early sensory processing, although these findings appear less consistent. More studies using these techniques to investigate neural processes in drug-exposed infants are warranted in order to understand how exposure may produce functional and/or structural changes in the brain.

3. Childhood and juvenile stages

Childhood may include the period between years 3 and 7 of age, with a juvenile stage between 7–10 years for girls and 12 years for boys (Del Giudice et al., 2009). The brain changes significantly throughout these periods, with overall growth and thickening of frontal and parietal areas (Sowell et al., 1999). This growth corresponds to the development of cognitive ability (Sowell et al., 2004). Prenatal exposure may influence these processes, possibly through altered compensatory development as a result of structural changes observed in infancy, as suggested by (Derauf et al., 2009). MRI investigations in childhood have revealed smaller gray-matter volumes in those with exposure to polysubstances (Walhovd et al., 2007), cocaine (Akyuz et al., 2014) and methamphetamine (Chang et al., 2004), and these reductions in gray matter are typically associated with cognitive deficits. Papers examining functional neural correlates of substance exposure in childhood are summarized in Table 2.

Three papers applied diffusion-tensor imaging (DTI) to examine white matter in children exposed to substances. FA and MD were examined in children between 3–4 years of age with and without prenatal methamphetamine exposure (Cloak et al., 2009). Children with prenatal methamphetamine exposure as compared to those without had lower diffusion-related measures (apparent diffusion coefficient; ADC) in white-matter tracts in frontal and parietal regions. When diffusivity was examined, higher FA values were found in left frontal regions. Older children with prenatal polysubstance exposure (predominantly

Table 2
Childhood.

Citation	Title	Exposure Type	Technique	Participants	Main Finding
Walhovd et al., 2010	White-matter characteristics and cognition in prenatally opiate- and polysubstance-exposed children: a diffusion tensor imaging study.	Polysubstance	DTI	14 polysubstance-exposed, 14 controls, 8.6-13.9 YOA	Exposed children showed lower FA in central, posterior, and inferior brain areas. FA was correlated positively with cognitive function in all groups.
Warner et al., 2006	Diffusion tensor imaging of frontal white matter and executive functioning in cocaine-exposed children.	Cocaine	DTI	28 PCE, 25 NDE, 10.6 YOA	Exposed children showed higher diffusion in left frontal callosal and right frontal projection fibers. They showed slower reaction times on a visual motor set shifting task and had lower scores on a verbal inhibition task. The amount of exposure was correlated with diffusion in left frontal callosal fibers and with task performance. Task performance was also correlated with FA in frontal areas.
Cloak et al., 2009	Lower diffusion in white matter of children with prenatal methamphetamine exposure	Methamphetamine	DTI	29 PME, 37 NDE, 3-4 YOA	Methamphetamine-exposed children showed lower ADC and FA in frontal and parietal areas.
Mayes et al., 2005	Event-related potentials in cocaine-exposed children during a Stroop task.	Cocaine	EEG	29 PCE, 29 NDE, 8 YOA	PCE children showed prolonged responses to words in a Stroop task. Effects were seen in the initial positive peak (P1), the second negative peak (N2) and the later positive peak (P3).
Boucher et al., 2014	Prenatal tobacco exposure and response inhibition in school-aged children: an event-related potential study.	Nicotine	EEG	186 children, 151 PTE, 35 NDE, 11.3 YOA	Tobacco-exposed children showed smaller amplitudes of the N2 and P3 components elicited by No-go stimuli. No-go P3 component amplitude was inversely correlated with externalizing problems and reported hyperactivity/impulsivity in school.
Whitham et al., 2015	Visual evoked potential latencies of three-year-old children prenatally exposed to buprenorphine or methadone compared with non-opioid exposed children: The results of a longitudinal study.	Opiates	EEG	11 PBE, 10 PME, 15 NDE, 3 YOA	There were no observed group differences in VEP latency.
Guo et al., 1994	Cognitive brain potential alterations in boys exposed to opiates: in utero and lifestyle comparisons.	Opiates	EEG	16 POE with opiate-using mothers, 14 non-POE with opiate-abusing mothers, 13 non-POE controls, 7-12 YOA	ERP alterations in P200 and memory test scores in those with and without exposure who lived with addicted mothers were similar.
Jones et al., 2004	Greater right frontal EEG asymmetry and nonemphathic behavior are observed in children prenatally exposed to cocaine.	Cocaine	EEG	27 PCE, 27 NDE, 3-6 YOA	PCE children showed greater right frontal EEG asymmetry, lessened empathy in response to a crying infant as well as their own mothers, and were less proficient at completing a cooperative task.
Sheinkopf et al., 2009	Functional MRI and response inhibition in children exposed to cocaine in utero. Preliminary findings.	Cocaine	FMRI	12 PCE, 12 NDE, 8-9 YOA	PCE children showed greater activation in the right inferior frontal cortex and caudate during a response inhibition task despite showing no behavioral differences.
Walhovd et al., 2007	Volumetric cerebral characteristics of children exposed to opiates and other substances in utero.	Polysubstance	MRI	14 Polysubstance-exposed (11.3 YOA), 14 NDE (9.8 YOA)	Substance-exposed children had smaller intracranial and brain volumes. Volumes were smaller in the pallidum and putamen in those with opiate exposure. Volumes of the right anterior cingulate, right lateral orbitofrontal cortex and the accumbens showed some associations with ability and questionnaire measures.
Chang et al., 2004	Smaller subcortical volumes and cognitive deficits in children with prenatal methamphetamine exposure.	Methamphetamine	MRI	13 PME (6.9 YOA), 15 NDE (7.8 YOA)	Methamphetamine-exposed children had lower scores on visual motor integration, attention, verbal memory and long-term spatial memory. They also showed smaller gray-matter volume in the bilateral putamen, the left and right globus pallidus, the left and right hippocampus and the bilateral caudate. The reduction in volume was correlated with performance on sustained attention and verbal memory tasks.
		Opiates	MRI		

(*continued on next page*)

Table 2 (*continued*)

Citation	Title	Exposure Type	Technique	Participants	Main Finding
Simes et al., 2017	Brain morphology in school-aged children with prenatal opioid exposure: A structural MRI study.			16 10-14-year-olds with POE, 16 non-exposed, 10-14 YOA	Reduced brain volume was seen in the basal ganglia, thalamus, and cerebellar white matter in the opioid-exposed group.
Simes et al., 2018	Functional MRI in prenatally opioid-exposed children during a working memory-selective attention task	Opiates	FMRI	11 with POE, 12 non-exposed, 10-14 YOA	Children with opioid exposure showed reduced accuracy and were slower to respond on the task. They also showed increased activation in prefrontal areas during the most demanding versions of the task compared to controls.
Akyuz et al., 2014	Structural brain imaging in children and adolescents following prenatal cocaine exposure: preliminary longitudinal findings.	Cocaine	MRI	11 PCE, 10 NCE 8-10 YOA scan 1, 13-15 YOA scan 2	PCE children showed smaller GM volumes in the cortex, thalamus and putamen, which correlated with amount of exposure. In a subgroup scanned again at 13-15 years, structures again were smaller in PCE.

YOA = Years of Age, POE = Prenatal opiate exposure, PCE = Prenatal cocaine exposure; NCE = Non-cocaine exposed prenatally with prenatal exposure to other substances, PME = prenatal methadone exposure, PBE = prenatal buprenorphine exposure, NDE = Non-drug exposed, MJ = Marijuana, VEP = visual evoked potential, ADC = Apparent Diffusion Coefficient, EEG = Electrophysiology, ERP = event related potential, Fmri = Functional Magnetic Resonance Imaging, DTI = Diffusion tensor imaging, FA = Fractional anisotropy, GM = Gray Matter.

opiates) also demonstrate white-matter differences when compared to non-exposed children (Walhovd et al., 2010). Specifically, clusters in multiple white-matter tracts in central, inferior, and posterior regions of the brain showed lower FA in *in utero* drug-exposed children than non-exposed children. Radial diffusion, more than axial diffusion, contributed to these differences. In addition, FA in the regions that differed between groups was related to intelligence.

Childhood behavior may relate to white-matter structure. Children (mean age 10 years) with and without *in utero* cocaine and poly-substance exposure performed executive-function tasks, including the Stroop and trail-making tasks, and underwent diffusion MRI (Warner et al., 2006). Higher diffusion (D_{av}, a measure of isotropic diffusion) was found in drug-exposed children in left frontal callosal and right frontal projection fibers. Moreover, average diffusion in left frontal callosal fibers was related to prenatal exposure to alcohol and marijuana, with the highest D_{av} values found for those children with exposure to both marijuana and cocaine. Significant correlations were also observed between performance on the executive function tasks and FA in areas of frontal white matter. Specifically, increased FA in left frontal callosal fibers was associated with better performance on the Stroop color-word task and on the Trail Making Test Part B. Just as in infancy, these findings suggest white-matter differences in childhood are related to *in utero* drug exposure, with findings in older childhood linked to cognitive performance.

EEG investigations into *in utero* drug-exposed children may be used to examine potential influences of exposure on specific neural processes. EEG evidence from investigations of the visual system indicates that, compared to findings during infancy, there are no longer sensory differences between children with and without *in utero* methadone exposure (Whitham et al., 2015). No amplitude or latency differences in VEPs were observed between 3-year-old individuals with and without *in utero* exposure to methadone or buprenorphine. However, other work in older children found that *in utero* exposure may impact processes related to emotional processing, executive functioning and/or impulse control. When exposed to emotional cues, such as infant cries and simulated maternal distress, and a frustrating task, PCE children aged 3–6 years (as compared to similarly aged children without *in utero* drug exposure) reacted less strongly to the infant crying and maternal distress stimuli, and were less effective at task completion (Jones et al., 2004). In addition, PCE children had greater right frontal EEG asymmetry, which may reflect increased frustration.

Another study examined EEG recordings during a cognitive control (Stroop task) in PCE children aged 7–9 years (Mayes et al., 2005). PCE as compared to non-drug-exposed children demonstrated slower responses to word stimuli and altered ERP amplitudes. PCE children had lower amplitudes and longer latencies of the initial positive peak (P1), the second negative peak (N2) and the later positive peak (P3). Thus, the EEG data suggest a neural foundation for reduced executive control and poorer emotional regulation in children with PCE.

Children with other types of exposure also demonstrate neural differences as indexed by EEG. In a study of Inuit children with prenatal tobacco exposure who performed a Go/No-Go task (Boucher et al., 2014), those with *in utero* exposure demonstrated no differences in behavior on the response-inhibition task, but did show smaller amplitudes of the inhibition-related N2 and P3 components. The amplitudes of these components were in turn related to behavioral reports of externalizing problems and hyperactivity in the classroom.

Response inhibition has also been examined in PCE children using fMRI (Sheinkopf et al., 2009). In a cohort of children aged 8–9 years, PCE children performed similarly to non-drug-exposed children with respect to error rates and reaction times, but showed different patterns of neural activations. PCE children showed greater activation in the right inferior frontal cortex and caudate during response inhibition, while non-drug-exposed children showed greater activations in temporal and occipital regions. These findings suggest that PCE may alter neural processes linked to impulsivity, involving greater recruitment of

Table 3
Adolescence.

Citation	Title	Exposure Type	Technique	Participants	Main Finding
Landi et al., 2017	Prenatal Cocaine Exposure Impacts Language and Reading Into Late Adolescence: Behavioral and ERP Evidence.	Cocaine	ERP	59 PCE (17.3 YOA), 51 NDE (16.8 YOA)	PCE-related deficits were observed across reading and language assessments, with reduced N1/P2 response and N400 response to sentence and word stimuli.
Banz et al., 2016	Gender-related Differences in Inhibitory Control and Sustained Attention among Adolescents with Prenatal Cocaine Exposure.	Cocaine	ERP	32 PCE, 15.07 YOA	No differences were found in risk-taking or ERP indices of risk-taking in regular trials. When frustration was induced, girls showed greater initial attention and boys showed greater sustained attention during attention trials.
Landi et al., 2012	Deviant ERP response to spoken non-words among adolescents exposed to cocaine in utero.	Cocaine	ERP	107 PCE, 46 NDE, 13 YOA	PCE related to altered ERP amplitude and latencies for ERPs related to language processing for the following components: N1/P2,N2, and P600
Zakiniaeiz et al., 2017	Altered functional connectivity to stressful stimuli in prenatally cocaine-exposed adolescents.	Cocaine/Poly other than heroin	FMRI	22 PCE (14.9 YOA), 22 (14.5 YOA) controls	PCE related to less connectivity in a parietal lobe cluster during a stress condition and more connectivity during a neutral/relaxing condition. Follow-up seed-based connectivity analyses revealed in PCE that the parietal seed positively connected to the inferior parietal and sensory areas and negatively connected to corticolimbic during both conditions. During the favorite-food condition, craving scores inversely correlated with corticolimbic connectivity in PCE subjects.
Roos et al., 2017	Effects of prenatal substance exposure on neurocognitive correlates of inhibitory control success and failure.	Cocaine	FMRI	7 polysubstance-exposed, 7 NDE, 13-17 YOA	PCE related to greater activation during inhibition in the right ventrolateral prefrontal cortex, right cuneus, and left inferior parietal lobe
Yip et al., 2016	Prenatal cocaine exposure, illicit-substance use and stress and craving processes during adolescence.	Cocaine/Poly other than heroin	FMRI	46 PCE (14.9 YOA), 22 NDE (14.5 YOA)	Among PCE subjects, Illicit-substance-use initiation was associated with decreased subcortical and increased cortical activity during the favorite-food condition; an opposite pattern was observed for the neutral/relaxing condition. Among PCE subjects, illicit-substance-use initiation associated with decreased activity in cortical and subcortical regions including amygdala, hippocampus and prefrontal cortex during the stress condition. Neural activity within cortico-striato-limbic regions negatively correlated with subjective ratings of anxiety and craving among those with illicit-substance use.
Yip et al., 2014a, 2014b	Prenatal cocaine exposure and adolescent neural responses to appetitive and stressful stimuli.	Cocaine	FMRI	22 PCE (14.9 YOA), 22 (14.5 YOA) controls	Among PCE subjects, reduced activity was observed during the favorite-food condition in cortical and subcortical brain regions, including the ventral striatum, anterior cingulate, and medial and dorslolateral PFC. No differences were observed for stress cues. Food craving was inversely related to dorsolateral PFC activation. Subjective anxiety ratings correlated inversely with activations in the orbitofrontal cortex and brainstem during the stress condition.
Muller et al., 2013	Altered reward processing in adolescents with prenatal exposure to maternal cigarette smoking.	Nicotine	FMRI	177 PTE, 177 NDE, 13-15 YOA	Among tobacco-exposed subjects, reduced response was observed in the ventral striatum during reward anticipation, but not reward receipt.
Jacobsen et al., 2006	Visuospatial memory deficits emerging during nicotine withdrawal in adolescents with prenatal exposure to active maternal smoking.	Nicotine	FMRI	35 PTE smokers (16.6 YOA), 26 NDE smokers (17.0 YOA)	PTE adolescent smokers showed greater nicotine-withdrawal-related deficits in immediate and delayed visuospatial memory, increased activation of left parahippocampal gyrus during early recognition testing of visuospatial stimuli, and increased activation of bilateral hippocampus during delayed recognition testing of visuospatial stimuli.
Schweitzer et al., 2015	Prenatal drug exposure to illicit drugs alters working memory-related brain activity and underlying network properties in adolescence.	Polysubstance	FMRI	27 PDE and 20 NDE 12-15 YOA	Polysubstance-exposed adolescents showed deactivations in the culmen during a visuo-spatial working memory task and no reaction time/culmen activation correlation. Network analysis showed lower global and local efficiency in polysubstance-exposure group.

(*continued on next page*)

Table 3 (*continued*)

Citation	Title	Exposure Type	Technique	Participants	Main Finding
Li et al., 2016	Longitudinal changes of amygdala and default mode activation in adolescents prenatally exposed to cocaine.	Cocaine	FMRI	21 PCE, 12 NDE, 14.3 YOA Time 1, 16.7 YOA time 2	Among PCE subjects, brain activations indicative of emotional arousal in the amygdala and default mode network did not show the reduction over time seen in non-exposed adolescents.
Bennett et al., 2009	Response inhibition among early adolescents prenatally exposed to tobacco: An fMRI study.	Nicotine	FMRI	7 PTE, 11 NDE, 12 YOA	Tobacco-exposed adolescents showed greater activation in the left frontal, right occipital, and bilateral temporal and parietal regions during the inhibition task, and reduced activation in the cerebellum during task performance.
Jacobsen et al., 2007a	Prenatal and Adolescent Exposure to Tobacco Smoke Modulates the Development of White Matter Microstructure.	Nicotine	DTI	25 PTE smokers, 8 PTE non-smokers, 14 NDE smokers, 20 NDE non-smokers, 13-18 YOA	Individuals with prenatal tobacco exposure and adolescent tobacco use showed increased FA in anterior cortical areas and the internal capsule. FA in the posterior limb of the left internal capsule positively correlated with reaction time during performance of an auditory attention task in smokers.
Rao et al., 2007	Altered resting cerebral blood flow in adolescents with in utero cocaine exposure revealed by perfusion functional MRI.	Cocaine	FMRI	24 PCE (14.4 YOA), 25 NDE (13.9 YOA)	Individuals with PCE showed significantly reduced cerebral blood flow in posterior and inferior brain regions, including occipital cortex and thalamus. Corrections for global blood flow exposed an increase in relative blood flow in anterior and superior brain regions, including the prefrontal, cingulate, insula, amygdala, and superior parietal cortex.
Hurt et al., 2008	Functional magnetic resonance imaging and working memory in adolescents with gestational cocaine exposure.	Cocaine	FMRI	17 PCE (14.7 YOA), 17 NDE (13.8 YOA)	Similar performances for PCE and NDE were found on an n-back task. Those with NDE showed proportionally greater activation in left prefrontal areas for the more difficult 2 back task.
Jacobsen et al., 2007b	Gender-specific effects of prenatal and adolescent exposure to tobacco smoke on auditory and visual attention.	Nicotine	FMRI	Full sample: 67 PTE smokers, 25 PTE nonsmokers, 44 NDE smokers, 45 NDE non-smokers Fmri sample: 24 PTE smokers, 7 PTE nonsmokers, 14 NDE smokers, 16 NDE non-smokers, 13-18 YOA	Among PTE females, reductions in auditory and visual attention were observed. Among PTE males, reductions in auditory attention were observed. Greater activation was seen in auditory brain regions for PTE individuals.
Li et al., 2013	Prenatal cocaine exposure alters functional activation in the ventral prefrontal cortex and its structural connectivity with the amygdala.	Cocaine	FMRI/DTI	33 PCE, 23 NDE in fMRI, 42 PCE, 31 NDE in DTI, 14 YOA	Among individuals with PCE, decreased vmPFC activation was found in response to increased memory load, along with increased amydgala activation. There were reduced white matter tracts between the vmPFC and amygdala and a lack of correlation between amygdala activation and vmPFC activation was seen in non-exposed participants.
Morie et al., 2018	Feedback processing in adolescents with prenatal cocaine exposure: an electrophysiologic investigation	Cocaine primarily, some polysubstance	EEG	49 PCE (17.6 YOA), 34 Non-exposed (3 mothers reported tobacco) (17.1 YOA)	Reduced P300 amplitude, localized to the dorsolateral prefrontal cortex using source localization procedures, was seen in the PCE group.
Morie et al., 2017	White matter crossing-fiber microstructure in adolescents prenatally exposed to cocaine.	Cocaine primarily, some polysubstance	DTI	39 PCE, 17 NDE, 14-16 YOA	There were no group differences for the whole brain. However, analyses in regions of interest using a crossing-fiber model revealed reduced anisotropy in secondary fibers in PCE individuals in the right cingulum and the left SLF, and increased anisotropy in the genu.
Geng et al., 2017	Long-term effects of prenatal drug exposure on the neural correlates of memory at encoding and retrieval.	Polysubstance	FMRI	19 PDE (specifically enrolled based on heroin and/or cocaine exposure, 18.2 YOA, 22 non-heroin-or-cocaine exposed (community controls) 17.1 YOA	Individuals with PDE remembered fewer items and showed changes in brain activation during memory encoding but not memory retrieval.

YOA = Years of age, PCE = Prenatal cocaine exposure, NCE = Non-cocaine exposed, PTE = Prenatal tobacco exposure, ME = prenatal methadone exposure, NDE = Non-drug exposed, MJ = Marijuana, VEP = visual evoked potential, AEF = Auditory Evoked Magnetic FielD, EEG = Electrophysiology, ERP = event related potential, SEF = Somatosensory evoked magnetic field, Fmri = Functional Magnetic Resonance Imaging, DTI = Diffusion tensor imaging, vmPFC = Ventromedial Prefrontal cortex, FA = Fractional anisotropy.

impulse-control-related circuitry (Chamberlain and Sahakian, 2007). Like the EEG study in children with prenatal tobacco exposure (Boucher et al., 2014), the effects of exposure in childhood may be relatively subtle with respect to behavior and may be more apparent at neural levels and more easily identified using imaging methods.

Structural and functional imaging studies in opiate-exposed children have also revealed differences. Sixteen opiate-exposed children between 10–14 years of age (childhood moving into adolescence) demonstrated reductions in brain volume in the basal ganglia, thalamus, and cerebellar white matter when compared to 16 non-exposed children (Sirnes et al., 2017). A subsample of this group, with 12 opiate-exposed and 11 non-exposed, also performed a working memory task using Stroop stimuli (Sirnes et al., 2018). The opiate-exposed children showed less accuracy and slower reaction times. In addition, opiate-exposed children showed greater activations in prefrontal areas than non-exposed children.

With respect to etiology, questions arise with regard to exposure and potentially long-lasting effects on childhood neural processing and behavior. Children with drug-using mothers may experience significant exposures to substances *in utero* which may contribute to behavioral or neural complications they may experience. In a study using EEG methodology (Guo et al., 1994), the authors examined three groups of children: one group consisted of 16 boys exposed to opiates *in utero* who lived with their opiate-abusing mothers, the second was a group of 14 boys who had no opiate exposure *in utero* but lived with opiate-abusing mothers, and the third consisted of 13 boys with no opiate-use exposure or opiate-using mothers (serving as a control group). Participants performed the Auditory Rare Event Monitoring Task and the Sternberg Memory Task while EEG was recorded, and behaviors and amplitudes of the P200 were compared across groups. The authors found that in both groups raised with opiate-abusing mothers, boys showed increased errors on the memory task and reduced amplitudes of the P200 when compared to control subjects. As the findings were similar across the prenatally exposed and non-exposed groups in the cohort raised by opiate-abusing mothers, data suggest that specific environmental factors, such as growing up with a drug abusing mother, may contribute importantly to observed findings independent of prenatal exposure. Speculatively, environmental influences may become more relevant over time as children mature into adolescence and young adulthood.

Imaging data suggest that children with prenatal substance exposure may have weaker regional brain connectivity, and ERP indices of cognitive control suggest poorer executive control. The few existing fMRI studies suggest no differences in performance on tasks of inhibitory control, and worse performance on tasks of working memory, relating to prenatal drug exposure. Observed increased activations suggest that children may be using more neural “effort” in order to perform fMRI tasks compared to non-exposed children in order to achieve comparable performance. This tendency may result in increased frustration with the tasks, although this possibility is speculative. Future work in children should investigate other domains such as emotional arousal and reward processing to examine how prenatal drug exposure may impact such processes in children.

4. Adolescence

Adolescence is a developmental stage that begins at puberty-onset, ranging typically from 10 to 12 years of age and ending approximately 5–10 years post-puberty, at roughly 18–20 for women and 21–25 for men (Coleman and Hendry, 1990). Adolescence is characterized by relatively increased impulsivity and risk-taking behaviors (Geier, 2013). Poor impulse regulation and increased reward motivation in adolescents may reflect an imbalance in the maturational trajectories of brain regions and circuits involved in reward-related motivational drives, such as the striatum, and brain regions and circuits involved in impulse regulation and behavioral control, like the prefrontal cortex (PFC) (Galvan, 2010; Galvan et al., 2006; Gogtay et al., 2004). These developmental brain factors may predispose adolescents to develop addictions and other psychiatric disorders (Chambers et al., 2003). The imbalance may reflect comparatively under-developed top-down control, coupled with greater motivational drives, resulting in heightened emotional reactivity and reward sensitivity (Geier et al., 2010). In adolescents and emerging adults, the influences of prenatal drug exposure may be particularly detrimental. PCE status has been associated with increased substance-use initiation in the early teen years of adolescence (Delaney-Black et al., 2011; Minnes et al., 2014), even when controlling for environmental factors (Richardson et al., 2013). Non-behaviorally based investigations into brain structure reveal altered blood flow in PCE adolescents (Rao et al., 2007) and alterations in white matter in prenatally tobacco-exposed adolescents (Jacobsen et al., 2007a) and in prenatally cocaine-exposed adolescents (Morie et al., 2017). It is important to understand the relationship between brain and behavior in prenatally drug-exposed adolescents. Twenty-one papers have examined neural functioning in prenatally drug-exposed adolescents, employing ERP and fMRI approaches. These papers are summarized in Table 3.

Adolescence is a time of drug-use experimentation, and adolescents with prenatal exposure tend to experiment with drugs at greater frequencies than prenatally non-drug-exposed individuals (Richardson et al., 2013). A potential complication of studies in this age range, especially in older adolescents, is determining if observed differences are attributable to prenatal exposure rather than to differences in the individuals’ own drug-use frequencies. Most researchers collect drug-use information from participants and covary for drug use in analyses. Nonetheless, it should be noted that it is rare for studies of PCE adolescents to be comprised entirely of non-drug-using participants.

Most investigations of prenatally drug-exposed adolescents have focused on reward processing and cognitive control, domains relevant to drug use. Using fMRI data from the IMAGEN sample, generated from several sites in different European countries (Schumann et al., 2010), the impact of prenatal exposure to maternal cigarette smoking was investigated in 177 13–15 year-old adolescents and 177 age- and sex-matched prenatally non-drug-exposed peers (Muller et al., 2013). All participants reported their own substance use and performed a monetary incentive delay task during fMRI. The monetary incentive delay task permits investigation of brain response to multiple stages (e.g., anticipation, outcome) of reward and loss processing (Knutson et al., 2001). Exposed adolescents reported more cigarette use; thus, lifetime cigarettes was used as a covariate. While there were no group differences for reward receipt, exposed adolescents showed reduced reward anticipation responses in the left and right ventral striatum. In addition, there were decreases in activation in prenatally tobacco-exposed adolescents in the middle frontal gyrus and the superior parietal cortex, regions previously implicated in reward processing. Areas, including the lingual, occipital and middle temporal gyri, previously implicated in visual processing and salience orientation, also showed reduced activation during reward anticipation. Together, these findings suggest important impacts of prenatal drug exposure on the neural underpinnings of reward processing, with implications for the development of addictions.

The neural correlates of the processing of appetitive and stressful states have also been examined in PCE adolescents. Specifically, a sample of 14-year-old PCE and prenatally non-drug-exposed adolescents performed a guided imagery fMRI task involving exposure to neutral-relaxing, stressful, or favorite-food conditions (Yip et al., 2014a). Similar to Muller et al. (2013), PCE as compared to non-drug-exposed adolescents had reduced activity in the ventral striatum during exposure to favorite-food cues; they also showed reduced activation in the anterior cingulate and medial and dorsolateral prefrontal cortices. In the same sample, a cluster in the parietal lobe showed less connectivity in PCE versus prenatally non-drug-exposed individuals during stressful conditions and more connectivity during neutral-relaxing conditions (Zakiniaeiz et al., 2017). This region showed differential

connectivity patterns with inferior parietal and sensory areas as well as cortico-limbic and medial pre-frontal areas across the PCE and prenatally non-drug-exposed individuals. In addition, food craving scores in PCE adolescents, but not in the prenatally non-drug-exposed adolescents, correlated with the degree of connectivity during the favorite-food condition. These two studies suggest that PCE may impact neural connectivity and processes related to reward processing into adolescence.

A third study by the same group examined the relationships between PCE status, substance-use initiation and neural activations related to the processing of neutral-relaxing, stressful, or favorite-food cues (Yip et al., 2016). Forty-six PCE and 22 prenatally non-drug-exposed adolescents were studied. Of the PCE sample, 39 of 46 participants reported substance use, as did 10 of the 22 prenatally non-drug-exposed participants. A significant three-way interaction was observed between substance-use initiation, PCE status and cue condition on neural responses in the bilateral insula and superior temporal gyrus. This interaction was related in part to PCE individuals who reported substance-use initiation showing greater decreases in activation in these regions during the favorite-food condition and greater activation during the neutral-relaxing condition. The findings suggest the importance of investigating further the influence of PCE exposure on neural activations linked to substance-use initiation given the relatively small sample studied to date.

This sample has also been investigated using EEG, with a focus on feedback processing (Morie et al., 2018). Thirty-nine adolescents with PCE and 17 non-exposed individuals performed a feedback task while EEG was recorded, and response feedback event-related potentials were examined. Feedback was impaired in the PCE sample, as evidenced by reduced amplitude of the P300. Source localization procedures localized the P300 to the dorsolateral-prefrontal cortex, implying reduced activity in this region during reward feedback in PCE individuals.

Other groups have examined arousal regulation in prenatally drug-exposed adolescents, especially with respect to PCE. Emotional reactivity was investigated in 33 PCE and 26 prenatally non-drug-exposed adolescents between the ages of 12–18 years, with a focus on functional connectivity between the ventromedial prefrontal cortex and the amygdala (Li et al., 2013). Structural connectivity between these two regions was also examined using diffusion imaging in 42 PCE and 31 prenatally non-drug-exposed adolescents. PCE adolescents performing an N-Back task with emotional distractors demonstrated decreased ventromedial prefrontal cortical activation, which correlated with increased amygdala activation. DTI findings revealed reduced structural connectivity between the ventromedial prefrontal cortex and the amygdala in the PCE group.

A follow-up study provides interesting insight into the development of neural circuitry related to emotional reactivity in PCE adolescents (Li et al., 2016). The authors examined the ventromedial prefrontal cortex and amygdala, as well as the default mode network, in 21 PCE and 12 prenatally non-drug-exposed adolescents at two time points—one when the individuals were at 14.3 years of age on average, and again when they were at 16.7 years of age on average. The findings revealed that brain activation in the amygdala, previously implicated in emotional arousal, as well as activation in the default mode network, was reduced at Time 2 for prenatally non-drug-exposed adolescents. However, there were no changes in these activities over time for the PCE group. Intriguingly, drug use was not different between groups, suggesting that these differences in emotional reactivity may reflect developmental ramifications of PCE. Caution is warranted in interpretation given the small sample size.

Response inhibition is another important cognitive process that may be disrupted in individuals with substance-use exposure. Two studies of prenatally drug-exposed adolescents have investigated the neural correlates of response inhibition. In 7 prenatally polysubstance-exposed and 7 prenatally non-drug-exposed adolescents between the ages of 13–17 years, exposed adolescents performing a Go/No-Go task showed increased activity during inhibition in the right ventrolateral prefrontal cortex, right cuneus, and left inferior parietal lobe, and reduced activation in the occipital lobe during an error (Roos et al., 2017). Response inhibition has also been examined in prenatally tobacco-exposed adolescents. During performance of a Go/No-Go task in 7 prenatally tobacco-exposed and 11 non-exposed 12-year-old youth (Bennett et al., 2009), whole-brain analyses revealed that prenatally tobacco-exposed children had greater activation in superior and inferior frontal brain areas and the anterior cingulate during inhibition trials. While the regions are not identical between these two studies, data suggest that substance exposure may impact neural correlates of response inhibition. This possibility has implications for inhibiting risk-taking behaviors and thus altering developmental trajectories.

The neural correlates of language processing have also been examined in PCE adolescents (Landi et al., 2017, 2012). In the first study, 107 PCE and 46 prenatally non-drug-exposed youth with a mean age of 13 years listened to nonsense words while ERP responses were recorded. PCE adolescents showed alterations in ERP indices of very early sensory processing (N1 and P2 components at approximately 100 ms), as well as alterations in indices of phonological processing (N2) and later processing (P600) considered to reflect higher level semantic or memory components. In a subsample of this cohort including 59 PCE and 51 prenatally non-drug-exposed adolescents tested at a mean age of 17 years, participants performed linguistic assessments of word reading, reading comprehension, and semantic and grammatical processing. Participants also performed a rhyme-priming task, a semantic-priming task, and a sentence-reading task while ERP was recorded. As participants were older and had reported some initiation of drug use, drug-use initiation was covaried. PCE participants showed worse performance on the linguistic assessments and atypical ERP responses including reduced N1/P2 responses (suggesting poorer phonological mapping) and reduced N400 responses (suggesting poorer semantic processing). Taken together, these two studies suggest that PCE may impact neural correlates of language processing in both early and later adolescence.

Working memory has also been examined in prenatally drug-exposed adolescents, although findings appear possibly inconsistent. When visuo-spatial working memory was examined in 12–15 year-old prenatally polydrug-exposed adolescents and prenatally non-drug-exposed adolescents (Schweitzer et al., 2015), activation differences in the left middle frontal gyrus and the culmen were observed. The prenatally non-drug-exposed adolescents showed activation in these regions that corresponded to task performance that was not seen in the drug-exposed adolescents. In addition, network node analysis suggested poorer connectivity in the prenatally drug-exposed adolescents. However, in 25 PCE adolescents who were aged 13–14 years and who performed an N-Back test, no group differences were observed relative to prenatally non-drug-exposed adolescents in either performance on the working memory tasks or in activation patterns during the task (Hurt et al., 2008).

Memory processing has been investigated in prenatally drug-exposed adolescents. One study (Jacobsen et al., 2006) examined visuospatial and verbal memory in adolescent smokers who had (n = 35, mean age 16.6 years) and had not (n = 26, mean age 17 years) been exposed to tobacco prenatally, effectively controlling for substance use. Participants performed a recognition test both while they were allowed to smoke at will and after 24 h of abstinence, at which time they also underwent fMRI. Those with prenatal exposure performed worse on the visuospatial memory task post-abstinence than did those with no exposure. In addition, those with prenatal exposure showed increased activation of the left parahippocampal gyrus and bilateral hippocampus. The findings suggest that prenatal tobacco exposure may have effects into adolescence that are independent of individuals' tobacco use.

Memory encoding and retrieval processes have been examined in 19 prenatally polydrug-exposed and 22 prenatally non-drug-exposed

adolescents between 17 and 18 years of age (Geng et al., 2017). No brain activation differences were observed in the memory retrieval stage. However, hippocampal activation differed between groups during memory encoding. The non-drug-exposed adolescents showed a greater difference in activation in the left hippocampus between remembered and non-remembered items, while the exposed group showed a greater difference in the right hemisphere. This finding suggests developmental differences in prenatally drug-exposed adolescents and potentially different neural underpinnings for cognitive strategies used during memory processes, although this study had certain limitations, including a small sample size and absence of covariation for participants' use of substances.

One important and at times overlooked factor in studies of prenatal drug exposure is gender. Data suggest that behavioral ramifications of prenatal drug exposure are more pronounced in males. As children mature into adolescence, males with PCE engage in more risk-taking behaviors, including those relating to substance use, violence, and aggression (Ackerman et al., 2010; Bennett et al., 2007; Chaplin et al., 2010, 2015). However, few (n = 3 to date) studies have examined neural correlates of behavior in prenatally drug-exposed individuals as a function of gender. In an ERP study of response inhibition in 15-year-old adolescents (Banz et al., 2016), PCE boys as compared to PCE girls demonstrated larger P3 amplitudes. Fifteen-year-old PCE males have been found to be more sensitive to reward feedback than similarly aged PCE females (Crowley et al., 2009). In 181 male and female adolescent smokers and nonsmokers with and without prenatal exposure to maternal smoking, 63 performed visual and auditory selective attention tasks while fMRI was recorded (Jacobsen et al., 2007b). While there were no gender-related differences in brain activations, effects were found for exposure. Activation of the right superior temporal gyrus and the left and right lingual gyrus was greater in the prenatally tobacco-exposed groups. However, behavioral analyses of performance on the visual and auditory attention tasks suggest that prenatal tobacco exposure may have had more deleterious effects on females' performance. More research is needed on gender-related differences as related to prenatal drug-exposure, particularly with respect to cognition, reward processing and risk-taking.

In summary, multiple studies have investigated cognitive processes in prenatally drug-exposed adolescents, revealing largely subtle deficits. Exposed adolescents performing executive and memory tasks tend not to show behavioral differences from their non-exposed peers, but often show increased activation in regions of the brain that underlie performance of the task. This may suggest a need for increased cognitive effort in drug-exposed adolescents to perform the task to the same standard as non-exposed adolescents. Neural correlates suggesting reduced reward responsiveness have also been observed. These findings raise questions regarding whether the observed differences may link to other clinically relevant characteristics like anhedonia. Differences in neural correlates of executive functioning and reward processing may lead to an increased risk for substance-use initiation and disorders associated with prenatal drug exposure.

5. Emerging adulthood

Emerging adulthood includes the period between 18–25 years of age when individuals in developing societies often begin to achieve independence but do not yet have a clearly defined role (Arnett, 2000). This life stage is relevant to substance-use progression; e.g., for college-attending individuals to begin patterns of binge-use (Daw et al., 2017). It is also an age range when experimentation with substances may progress to addictions (Sussman and Arnett, 2014).

Relatively few studies have examined prenatal drug exposure in emerging adulthood, and those that do have typically examined tobacco and marijuana exposure and used fMRI. They are summarized in Table 4. All but one study are from the Ottawa Prenatal Prospective Study (the OPPS sample). This sample, recruited beginning in 1978, consists of individuals who were exposed to marijuana or tobacco *in utero* and were followed for over two-and-a-half decades. The other study used data from the Mannheim Study of Children at Risk, which is an ongoing epidemiological cohort study of the long-term outcome of early risk factors, including parental substance use, in Germany.

Examining inhibitory control and executive functioning is a common goal of the research in this age range. Longo et al. (Longo et al., 2013) investigated inhibitory control using a Go/No-Go task in 25 emerging adults (12 of whom had prenatal tobacco exposure) at the mean age of 21 years and found that those with exposure showed greater activation in the inferior frontal gyrus, anterior cingulate cortex, thalamus and inferior parietal lobule, as well as in the basal ganglia and the posterior cerebellum, despite showing no behavioral differences and when covarying for participant substance use. Verbal working memory has also been examined in this same sample (Longo et al., 2014). Participants performed a 2-Back working memory task. Despite similar task performance, prenatal tobacco exposure was associated with greater activity in the middle frontal gyrus, precentral gyrus, inferior parietal lobe and cingulate gyrus.

Response inhibition has also been examined in individuals with prenatal marijuana exposure in the OPPS sample (Smith et al., 2004). Thirty-one 18- to 22-year-olds, 16 of whom had prenatal marijuana exposure, performed a Go/No-Go task during fMRI. Unlike the prenatally tobacco-exposed individuals, those with prenatal marijuana exposure performed worse on the task, making more commission errors. Exposed participants, even when covarying for individual use, showed an increase in neural activity in bilateral prefrontal cortex and right premotor cortex during inhibitions. Prenatal exposure to marijuana was also associated with decreased activity in the left cerebellum. During performance of a visuospatial working-memory task, relatively increased activation in the left inferior and middle frontal gyri, left parahippocampal gyrus, left middle occipital gyrus and left cerebellum was observed as a function of prenatal marijuana exposure (Smith et al., 2006a).

In another study of this sample, the relationships between prenatal marijuana exposure and multiple facets of executive function were examined (Smith et al., 2016). The authors reported on previous data along with data from two new investigations of working memory using letter cues and conflict processing with a counting Stroop task. Sixteen participants between the ages of 18 and 22 years were prenatally exposed to marijuana while 15 had no prenatal marijuana exposure. There were no behavioral differences noted aside from the previously reported difference in commission errors during the Go/No-Go task. However, even when covarying for individual marijuana use, there were differences in activation between groups. A consistent finding was increased activity in posterior regions in the prenatally exposed group during performance of the new tasks. During the letter 2-back task, exposed individuals revealed increased activation in the left middle occipital gyrus, cerebellum and the right superior temporal gyrus. Exposed individuals also showed more activation in the left cuneus and right superior frontal gyrus during the counting Stroop task.

A recent study (Willford et al., 2018) examined neural activation during an attention task in 21-year-old individuals recruited from the Maternal Health Practices and Child Development (MHPCD) Project. Participants had either cocaine and polysubstance exposure (including marijuana, tobacco, and alcohol, N = 15) polysubstance exposure (N = 17) or no exposure (15 non-exposed controls). Participants performed the attention network task, one that investigates three major phases of attention: Alerting, orienting, and executive function. While fronto-parietal attentional network activation was observed in both groups, there were no group differences in activation, nor were there groups differences in performance. This is surprising considering previous literature, although it should be noted that the authors did not have biological measures for prenatal use.

There is one study of young adults at an older age. From the Mannheim sample, 178 young adults at a mean age of 25 years, 73 of

Table 4
Emerging/Young Adulthood.

Citation	Title	Exposure Type	Technique	Participants	Main Finding
Holz et al., 2014	Effect of prenatal exposure to tobacco smoke on inhibitory control: neuroimaging results from a 25-year prospective study.	Nicotine	FMRI	38 PTE, 140 NDE, 25 YOA	Those with tobacco exposure showed reduced responses in the anterior cingulate, the right and left inferior frontal gyrus, and the supramarginal gyrus during inhibitions. An inverse relationship was present between inferior frontal gyrus activity and ADHD symptoms and between anterior cingulate cortex activity and novelty seeking.
Smith et al., 2004	Effects of prenatal marijuana on response inhibition: an fMRI study of young adults	Marijuana	FMRI	16 prenatal MJ-exposed, 15 NDE, 18-22 YOA	Those with MJ exposure showed increased activity in the bilateral prefrontal cortex and the right premotor cortex during response inhibitions. They also showed a reduction in cerebellum activation, and made more errors of commission.
Smith et al., 2006a, 2006b	Effects of prenatal marijuana on visuospatial working memory: An fMRI study in young adults	Marijuana	FMRI	16 prenatal MJ-exposed, 15 NDE, 18-22 YOA	Those with MJ exposure showed no significant performance differences, but did show increased activity in the left inferior and middle frontal gyri, the left parahippocampal gyrus, the left middle occipital gyrus and the left cerebellum that correlated with level of exposure. They also showed less activity in the right inferior and middle frontal gyri.
Longo et al., 2013	The long-term effects of prenatal nicotine exposure on response inhibition: An fMRI study of young adults	Nicotine	FMRI	12 prenatal nicotine exposed, 13 NDE, 21 YOA	Those with nicotine exposure showed similar performance on the task, and showed greater activity in the inferior frontal gyrus, the inferior parietal lobe, the thalamus, the basal ganglia, and the posterior cerebellum.
Longo et al., 2014	The long-term effects of prenatal nicotine exposure on verbal working memory: An fMRI study of young adults	Nicotine	FMRI	12 prenatal nicotine-exposed, 13 NDE, 21 YOA	Those with nicotine exposure showed similar performance on the task, and showed greater activity in the middle frontal gyrus, the precentral gyrus, the inferior parietal lobe, and the cingulate gyrus.
Willford et al., 2018	An examination of the association between prenatal cocaine exposure and brain activation measures of arousal and attention in young adults: An fMRI study using the Attention Network Task	Polysubstance	FMRI	15 prenatally exposed to cocaine, MJ, Alcohol or tobacco,17 exposed to MJ, Alcohol or Tobacco, 15 Control, 21 YOA	No group differences in behavior (accuracy or reaction time) were found during the attention task. Fronto-parietal networks were identified that were active during the attention-orienting task. However, no group differences were found in activation.
Smith et al., 2016	Prenatal marijuana exposure impacts executive functioning into young adulthood: An fMRI study	Marijuana	FMRI	16 prenatal MJ-exposed, 15 Non-MJ-exposed with some nicotine and alcohol exposure, 18-22 YOA	The authors reviewed four tasks. Exposed individuals demonstrated similar performance, and consistently showed altered blood flow and a pattern of increased left posterior activity.

YOA = Years of Age, PTE = Prenatal tobacco exposure, PCE = Prenatal cocaine exposure, NDE = Non-drug exposed, MJ = Marijuana, Fmri = Functional Magnetic Resonance Imaging, ADHD = Attention deficit hyperactivity disorder.

whom had been exposed to tobacco prenatally, performed a Go/No-Go flanker task (Holz et al., 2014). Information was collected about lifetime symptoms of attention-deficit/hyperactivity disorder and lifetime use of tobacco. When these variables were covaried, there was no indication of behavioral differences, but exposed individuals evidenced reduced, not increased, activation in the anterior cingulate, supramarginal gyrus and inferior frontal gyrus. Potential differences between findings from this study and others described above may be related to the age of the participants, the presence of ADHD (attention-deficit/hyperactivity disorder) symptoms, the task used, greater number of participants or other factors.

The generally increased activation in exposed individuals in all but two studies suggests that marijuana and tobacco exposure may result in increased required effort on executive function tasks, at least at the ages studied (18–22 years), which is similar to the increased activation seen during executive and memory tasks in adolescents. However, there are null findings (Willford et al., 2018), and more research in this age range should be performed. In addition, more research is necessary on individuals similarly aged as in the Holz et al. study (2014) to elucidate how activation during performance of executive tasks may change as prenatally drug-exposed individuals mature into adulthood. In addition, it will be important to investigate reward processing in emerging adults to investigate if differences seen in the neural correlates of reward processing in adolescence persist into adulthood, and if so, what may be the clinical and public health implications.

6. Conclusions

Exposure to drugs of abuse *in utero* may have long-lasting, albeit subtle, effects on cognition, notably in processes related to executive function, memory, and reward processing. Altered connectivity, with hyperconnectivity noted in frontal regions and hypoconnectivity noted in subcortical regions (Grewen et al., 2015; Salzwedel et al., 2016, 2015), has been seen in infancy. In childhood, diffusion data suggest white-matter deficits (Colby et al., 2012), and the preponderance of data from fMRI and ERP studies suggest that children (especially males) show behavioral concerns that may relate to differences in the neural correlates of executive-function processes (Boucher et al., 2014; Fisher et al., 2011; Mayes et al., 2005; Sheinkopf et al., 2009) and increased frustration when performing tasks (Jones et al., 2004). The extent to which these findings may relate to patterns of altered connectivity seen in infancy requires additional investigation. In adolescence, multiple studies find that prenatally drug-exposed individuals have altered brain activations that may relate to inhibition (Bennett et al., 2009; Roos et al., 2017) and working memory (Hurt et al., 2008; Jacobsen et al., 2006; Schweitzer et al., 2015), suggesting that more cognitive effort may need to be exerted to perform executive tasks at comparable levels. In addition, the few studies that have examined reward processing in adolescents suggest blunted activations during processing of monetary (Muller et al., 2013) and food (Yip et al., 2016, 2014b) rewards, consistent with reward-deficit theories of addiction and addiction vulnerability (Blum et al., 2000). Altered connectivity between reward-related brain regions have also been reported (Li et al., 2016), which is notable because adolescents with prenatal drug exposure may turn to more intense sources of reward and thus be particularly vulnerable to substance-use initiation and addiction. The findings appear to resonate with hypoconnectivity of reward-related brain areas observed in infancy relative to prenatal drug exposure. Prenatally drug-exposed adolescents may also demonstrate effects, either behaviorally or at neural levels of processing, with respect to language processing (Landi et al., 2017, 2012) and memory encoding (Geng et al., 2017). Increased cognitive effort to perform at normal levels may result in frustration throughout the lifespan that increases stress and leads to use of other substances, although this notion is largely speculative. As the Guo et al. (1994) study suggests, neural changes relating to prenatal drug exposure may also coincide with environmental impacts of growing up with a substance-abusing parent, and environmental influences may become increasingly relevant as children mature. As adolescents mature into emerging adulthood, the pattern of increased neural activation, possibly reflecting increased neural effort, remains during response inhibition (Longo et al., 2013; Smith et al., 2004, 2016) and working memory (Longo et al., 2014; Smith et al., 2006a) tasks. The preponderance of data suggest that prenatal exposure to substances is marked by a reduction in activation of reward systems and alterations in the neural processes underlying executive functioning processes that may prove frustrating for individuals.

7. Future directions

More research is needed into prenatal drug exposure. Most work has involved adolescents, and additional efforts should focus on other life stages. These stages include infancy and childhood where interventions may be most beneficial and in emerging adulthood when individuals are tasked with becoming independent and are more likely to increase their use of substances, often to detrimental levels. The dearth of literature in these age ranges should be addressed. Propensities to develop problems with non-substance addictions (e.g., gambling, gaming) in prenatally exposed individuals also warrant investigation. The prevalence of poly-substance use by mothers complicates precise determination regarding which substances may be most impactful on progeny. Studies that examine exposure to specific substances and use large samples could be highly informative. Finally, given gender-related differences in behavior in prenatally drug-exposed individuals, studies should consider gender in examinations in order to determine if exposure to specific substances may exert deleterious effects in gender-specific fashions.

Role of Funding Source

Funding for this work included National Institute of Health grants, K01 DA034125 (MJC), T32 MH018268 (MJC), P50 DA09241, UL1-DE19586, RL1 AA017539, R01 DA006025, R01 DA017863, K05 DA020091; T32 DA007238 and R21 DA030665. KPM receives support from MH018268-31 and from K01DA042937. MNP receives support from R01 DA035058, R01 DA039136, and the Connecticut Council on Problem Gambling, and the Connecticut Department of Mental Health and Addiction Services. Beyond funding, the funding agencies had no further role in the writing of the report or in the decision to submit the paper for publication.

Contributors

Dr. Morie wrote the first draft of the paper and worked with co-authors on subsequent drafts. All authors contributed to the editorial process and have approved the final submitted version of the manuscript.

Conflict of interest

The authors report no conflict of interest with respect to the content of this manuscript.

Dr. Potenza has consulted for and advised Shire, Rivermend Health, Opiant/Lightlake Therapeutics and Jazz Pharmaceuticals; received research support (to Yale) from the Mohegan Sun Casino and the National Center for Responsible Gaming; participated in surveys, mailings, or telephone consultations related to drug addiction, impulse control disorders or other health topics; consulted for and/or advised legal and gambling entities on issues related to impulse control and addiction; provided clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; performed grant reviews for the National Institutes of Health and other agencies; has guest-edited journal sections; given academic lectures in grand

rounds, CME events and other clinical/scientific venues; and generated books or chapters for publishers of mental health texts. The other authors report no financial relationships with commercial interests.

References

Ackerman, J.P., Riggins, T., Black, M.M., 2010. A review of the effects of prenatal cocaine exposure among school-aged children. Pediatrics 125, 554–565.

Akyuz, N., Kekatpure, M.V., Liu, J., Sheinkopf, S.J., Quinn, B.T., Lala, M.D., Kennedy, D., Makris, N., Lester, B.M., Kosofsky, B.E., 2014. Structural brain imaging in children and adolescents following prenatal cocaine exposure: preliminary longitudinal findings. Dev. Neurosci. 36, 316–328.

Arnett, J.J., 2000. Emerging adulthood - a theory of development from the late teens through the twenties. Am. Psychol. 55, 469–480.

Banz, B.C., Wu, J., Crowley, M.J., Potenza, M.N., Mayes, L.C., 2016. Gender-related differences in inhibitory control and sustained attention among adolescents with prenatal cocaine exposure. Yale J. Biol. Med. 89, 143–151.

Basser, P.J., Pierpaoli, C., 1996. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J. Magn. Reson. B 111, 209–219.

Bell, M.A., Cuevas, K., 2012. Using EEG to study cognitive development: issues and practices. J. Cogn. Dev. 13, 281–294.

Bennett, D., Bendersky, M., Lewis, M., 2007. Preadolescent health risk behavior as a function of prenatal cocaine exposure and gender. J. Dev. Behav. Pediatr. 28, 467–472.

Bennett, D.S., Mohamed, F.B., Carmody, D.P., Bendersky, M., Patel, S., Khorrami, M., Faro, S.H., Lewis, M., 2009. Response inhibition among early adolescents prenatally exposed to tobacco: an fMRI study. Neurotoxicol. Teratol. 31, 283–290.

Blum, K., Braverman, E.R., Holder, J.M., Lubar, J.F., Monastra, V.J., Miller, D., Lubar, J.O., Chen, T.J., Comings, D.E., 2000. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J. Psychoactive Drugs 32, 1–112.

Boucher, O., Jacobson, J.L., Burden, M.J., Dewailly, E., Jacobson, S.W., Muckle, G., 2014. Prenatal tobacco exposure and response inhibition in school-aged children: an event-related potential study. Neurotoxicol. Teratol. 44, 81–88.

Chamberlain, S.R., Sahakian, B.J., 2007. The neuropsychiatry of impulsivity. Curr. Opin. Psychiatry 20, 255–261.

Chambers, R.A., Taylor, J.R., Potenza, M.N., 2003. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. Am. J. Psychiatry 160, 1041–1052.

Chang, L., Smith, L.M., LoPresti, C., Yonekura, M.L., Kuo, J., Walot, I., Ernst, T., 2004. Smaller subcortical volumes and cognitive deficits in children with prenatal methamphetamine exposure. Psychiatry Res. 132, 95–106.

Chang, L., Oishi, K., Skranes, J., Buchthal, S., Cunningham, E., Yamakawa, R., Hayama, S., Jiang, C.S., Alicata, D., Hernandez, A., Cloak, C., Wright, T., Ernst, T., 2016. Sex-specific alterations of white matter developmental trajectories in infants with prenatal exposure to methamphetamine and tobacco. JAMA Psychiat. 73, 1217–1227.

Chaplin, T.M., Freiburger, M.B., Mayes, L.C., Sinha, R., 2010. Prenatal cocaine exposure, gender, and adolescent stress response: a prospective longitudinal study. Neurotoxicol. Teratol. 32, 595–604.

Chaplin, T.M., Visconti, K.J., Molfese, P.J., Susman, E.J., Klein, L.C., Sinha, R., Mayes, L.C., 2015. Prenatal cocaine exposure differentially affects stress responses in girls and boys: associations with future substance use. Dev. Psychopathol. 27, 163–180.

Cloak, C.C., Ernst, T., Fujii, L., Hedemark, B., Chang, L., 2009. Lower diffusion in white matter of children with prenatal methamphetamine exposure. Neurology 72, 2068–2075.

Colby, J.B., Smith, L., O'Connor, M.J., Bookheimer, S.Y., Van Horn, J.D., Sowell, E.R., 2012. White matter microstructural alterations in children with prenatal methamphetamine/polydrug exposure. Psychiatry Res. 204, 140–148.

Coleman, J.C., Hendry, L.B., 1990. The Nature of Adolescence. Routledge, London; New York.

Crowley, M.J., Wu, J., Crutcher, C., Bailey, C.A., Lejuez, C.W., Mayes, L.C., 2009. Risk-taking and the feedback negativity response to loss among at-risk adolescents. Dev. Neurosci. 31, 137–148.

Daw, J., Margolis, R., Wright, L., 2017. Emerging adulthood, emergent health lifestyles: sociodemographic determinants of trajectories of smoking, binge drinking, obesity, and sedentary behavior. J. Health Soc. Behav. 58, 181–197.

Del Giudice, M., Angeleri, R., Manera, V., 2009. The juvenile transition: a developmental switch point in human life history. Dev. Rev. 29, 1–31.

Delaney-Black, V., Chiodo, L.M., Hannigan, J.H., Greenwald, M.K., Janisse, J., Patterson, G., Huestis, M.A., Partridge, R.T., Ager, J., Sokol, R.J., 2011. Prenatal and postnatal cocaine exposure predict teen cocaine use. Neurotoxicol. Teratol. 33, 110–119.

Derauf, C., Kekatpure, M., Neyzi, N., Lester, B., Kosofsky, B., 2009. Neuroimaging of children following prenatal drug exposure. Semin. Cell Dev. Biol. 20, 441–454.

Fisher, P.A., Lester, B.M., DeGarmo, D.S., Lagasse, L.L., Lin, H., Shankaran, S., Bada, H.S., Bauer, C.R., Hammond, J., Whitaker, T., Higgins, R., 2011. The combined effects of prenatal drug exposure and early adversity on neurobehavioral disinhibition in childhood and adolescence. Dev. Psychopathol. 23, 777–788.

Frank, D.A., Augustyn, M., Knight, W.G., Pell, T., Zuckerman, B., 2001. Growth, development, and behavior in early childhood following prenatal cocaine exposure: a systematic review. JAMA 285, 1613–1625.

Galvan, A., 2010. Adolescent development of the reward system. Front. Hum. Neurosci. 4, 6.

Galvan, A., Hare, T.A., Parra, C.E., Penn, J., Voss, H., Glover, G., Casey, B.J., 2006. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. J. Neurosci. 26, 6885–6892.

Geier, C.F., 2013. Adolescent cognitive control and reward processing: implications for risk taking and substance use. Horm. Behav. 64, 333–342.

Geier, C.F., Terwilliger, R., Teslovich, T., Velanova, K., Luna, B., 2010. Immaturities in reward processing and its influence on inhibitory control in adolescence. Cereb. Cortex 20, 1613–1629.

Geng, F., Salmeron, B.J., Ross, T.J., Black, M.M., Riggins, T., 2017. Long-term effects of prenatal drug exposure on the neural correlates of memory at encoding and retrieval. Neurotoxicol. Teratol. 65, 70–77.

Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., Vaituzis, A.C., Nugent, T.F., Herman, D.H., Clasen, L.S., Toga, A.W., Rapoport, J.L., Thompson, P.M., 2004. Dynamic mapping of human cortical development during childhood through early adulthood. Proc. Natl. Acad. Sci. U. S. A. 101, 8174–8179.

Goldie, W.D., 1992. The brainstem auditory evoked potential in infants and children. J. Clin. Neurophysiol. 9, 394–407.

Grewen, K., Salzwedel, A.P., Gao, W., 2015. Functional connectivity disruption in neonates with prenatal marijuana exposure. Front. Hum. Neurosci. 9, 601.

Guo, X.Y., Spencer, J.W., Suess, P.E., Hickey, J.E., Better, W.E., Herning, R.I., 1994. Cognitive brain potential alterations in boys exposed to opiates - in-utero and lifestyle comparisons. Addict. Behav. 19, 429–441.

Hansen, R.L., Struthers, J.M., Gospe, S.M., 1993. Visual-evoked potentials and visual processing in stimulant drug-exposed infants. Dev. Med. Child Neurol. 35, 798–805.

Holz, N.E., Boecker, R., Baumeister, S., Hohm, E., Zohsel, K., Buchmann, A.F., Blomeyer, D., Jennen-Steinmetz, C., Hohmann, S., Wolf, I., Plichta, M.M., Meyer-Lindenberg, A., Banaschewski, T., Brandeis, D., Laucht, M., 2014. Effect of prenatal exposure to tobacco smoke on inhibitory control: neuroimaging results from a 25-year prospective study. JAMA Psychiat. 71, 786–796.

Hurt, H., Giannetta, J.M., Korczykowski, M., Hoang, A., Tang, K.Z., Betancourt, L., Brodsky, N.L., Shera, D.M., Farah, M.J., Detre, J.A., 2008. Functional magnetic resonance imaging and working memory in adolescents with gestational cocaine exposure. J. Pediatr. 152, 371–377.

Jacobsen, L.K., Slotkin, T.A., Westerveld, M., Mencl, W.E., Pugh, K.R., 2006. Visuospatial memory deficits emerging during nicotine withdrawal in adolescents with prenatal exposure to active maternal smoking. Neuropsychopharmacology 31, 1550–1561.

Jacobsen, L.K., Picciotto, M.R., Heath, C.J., Frost, S.J., Tsou, K.A., Dwan, R.A., Jackowski, M.P., Constable, R.T., Mencl, W.E., 2007a. Prenatal and adolescent exposure to tobacco smoke modulates the development of white matter microstructure. J. Neurosci. 27, 13491–13498.

Jacobsen, L.K., Slotkin, T.A., Mencl, W.E., Frost, S.J., Pugh, K.R., 2007b. Gender-specific effects of prenatal and adolescent exposure to tobacco smoke on auditory and visual attention. Neuropsychopharmacology 32, 2453–2464.

Johnson, C.P., Blasco, P.A., 1997. Infant growth and development. Pediatr. Rev. 18, 224–242.

Jones, N.A., Field, T., Davalos, M., Hart, S., 2004. Greater right frontal EEG asymmetry and nonemphathic behavior are observed in children prenatally exposed to cocaine. Int. J. Neurosci. 114, 459–480.

Kivisto, K., Nevalainen, P., Lauronen, L., Tupola, S., Pihko, E., Kivitie-Kallio, S., 2015. Somatosensory and auditory processing in opioid-exposed newborns with neonatal abstinence syndrome: a magnetoencephalographic approach. J. Matern. Fetal Neonatal Med. 28, 2015–2019.

Knutson, B., Fong, G.W., Adams, C.M., Varner, J.L., Hommer, D., 2001. Dissociation of reward anticipation and outcome with event-related fMRI. Neuroreport 12, 3683–3687.

Landi, N., Crowley, M.J., Wu, J., Bailey, C.A., Mayes, L.C., 2012. Deviant ERP response to spoken non-words among adolescents exposed to cocaine in utero. Brain Lang. 120, 209–216.

Landi, N., Avery, T., Crowley, M.J., Wu, J., Mayes, L., 2017. Prenatal cocaine exposure impacts language and reading into late adolescence: behavioral and ERP evidence. Dev. Neuropsychol. 42, 369–386.

Li, Z.H., Santhanam, P., Coles, C.D., Lynch, M.E., Hamann, S., Peltier, S., Hu, X.P., 2013. Prenatal cocaine exposure alters functional activation in the ventral prefrontal cortex and its structural connectivity with the amygdala. Psychiatry Res. 213, 47–55.

Li, Z.H., Coles, C.D., Lynch, M.E., Luo, Y.J., Hu, X.P., 2016. Longitudinal changes of amygdala and default mode activation in adolescents prenatally exposed to cocaine. Neurotoxicol. Teratol. 53, 24–32.

Longo, C.A., Fried, P.A., Cameron, I., Smith, A.M., 2013. The long-term effects of prenatal nicotine exposure on response inhibition: an fMRI study of young adults. Neurotoxicol. Teratol. 39, 9–18.

Longo, A., P, A.F, Cameron, I., A, M.S, 2014. The long-term effects of prenatal nicotine exposure on verbal working memory: an fMRI study of young adults. Drug Alcohol Depend. 144, 61–69.

Mayes, L.C., Molfese, D.L., Key, A.P., Hunter, N.C., 2005. Event-related potentials in cocaine-exposed children during a stroop task. Neurotoxicol. Teratol. 27, 797–813.

Minnes, S., Singer, L., Min, M.O., Wu, M.A.P., Lang, A., Yoon, S., 2014. Effects of prenatal cocaine/polydrug exposure on substance use by age 15. Drug Alcohol Depend. 134, 201–210.

Morie, K.P., Yip, S.W., Zhai, Z.W., Xu, J., Hamilton, K.R., Sinha, R., Mayes, L.C., Potenza, M.N., 2017. White-matter crossing-fiber microstructure in adolescents prenatally exposed to cocaine. Drug Alcohol Depend. 174, 23–29.

Morie, K.P., Wu, J., Landi, N., Potenza, M.N., Mayes, L.C., Crowley, M.J., 2018. Feedback processing in adolescents with prenatal cocaine exposure: an electrophysiological investigation. Dev. Neuropsychol. 43, 183–197.

Muller, K.U., Mennigen, E., Ripke, S., Banaschewski, T., Barker, G.J., Buchel, C., Conrod, P., Fauth-Buhler, M., Flor, H., Garavan, H., Heinz, A., Lawrence, C., Loth, E., Mann, K., Martinot, J.L., Pausova, Z., Rietschel, M., Strohle, A., Struve, M., Walaszek, B., Schumann, G., Paus, T., Smolka, M.N., Consortium, I., 2013. Altered reward

processing in adolescents with prenatal exposure to maternal cigarette smoking. JAMA Psychiat. 70, 847–856.
Neil, J.J., Smyser, C.D., 2018. Recent advances in the use of MRI to assess early human cortical development. J. Magn. Reson. 293, 56–69.
Paul, J.A., Logan, B.A., Krishnan, R., Heller, N.A., Morrison, D.G., Pritham, U.A., Tisher, P.W., Troese, M., Brown, M.S., Hayes, M.J., 2014. Development of auditory event-related potentials in infants prenatally exposed to methadone. Dev. Psychobiol. 56, 1119–1128.
Rao, H., Wang, J., Giannetta, J., Korczykowski, M., Shera, D., Avants, B.B., Gee, J., Detre, J.A., Hurt, H., 2007. Altered resting cerebral blood flow in adolescents with in utero cocaine exposure revealed by perfusion functional MRI. Pediatrics 120, E1245–E1254.
Richardson, G.A., Larkby, C., Goldschmidt, L., Day, N.L., 2013. Adolescent initiation of drug use: effects of prenatal cocaine exposure. J. Am. Acad. Child Psychiatry 52, 37–46.
Roos, L.E., Beauchamp, K.G., Pears, K.C., Fisher, P.A., Berkman, E.T., Capaldi, D., 2017. Effects of prenatal substance exposure on neurocognitive correlates of inhibitory control success and failure. Appl. Neuropsych.-Chil. 6, 269–280.
Salzwedel, A.P., Grewen, K.M., Vachet, C., Gerig, G., Lin, W., Gao, W., 2015. Prenatal drug exposure affects neonatal brain functional connectivity. J. Neurosci. 35, 5860–5869.
Salzwedel, A.P., Grewen, K.M., Goldman, B.D., Gao, W., 2016. Thalamocortical functional connectivity and behavioral disruptions in neonates with prenatal cocaine exposure. Neurotoxicol. Teratol. 56, 16–25.
Scher, M.S., Richardson, G.A., Robles, N., Geva, D., Goldschmidt, L., Dahl, R.E., Sclabassi, R.J., Day, N.L., 1998. Effects of prenatal substance exposure: altered maturation of visual evoked potentials. Pediatr. Neurol. 18, 236–243.
Scher, M.S., Richardson, G.A., Day, N.L., 2000. Effects of prenatal cocaine/crack and other drug exposure on electronencephalographic sleep studies at birth and one year. Pediatrics 105.
Schumann, G., Loth, E., Banaschewski, T., Barbot, A., Barker, G., Buchel, C., Conrod, P.J., Dalley, J.W., Flor, H., Gallinat, J., Garavan, H., Heinz, A., Itterman, B., Lathrop, M., Mallik, C., Mann, K., Martinot, J.L., Paus, T., Poline, J.B., Robbins, T.W., Rietschel, M., Reed, L., Smolka, M., Spanagel, R., Speiser, C., Stephens, D.N., Strohle, A., Struve, M., consortium, I., 2010. The IMAGEN study: reinforcement-related behaviour in normal brain function and psychopathology. Mol. Psychiatry 15, 1128–1139.
Schweitzer, J.B., Riggins, T., Liang, X., Gallen, C., Kurup, P.K., Ross, T.J., Black, M.M., Nair, P., Salmeron, B.J., 2015. Prenatal drug exposure to illicit drugs alters working memory-related brain activity and underlying network properties in adolescence. Neurotoxicol. Teratol. 48, 69–77.
Sheinkopf, S.J., Lester, B.M., Sanes, J.N., Eliassen, J.C., Hutchison, E.R., Seifer, R., LaGasse, L.L., Durston, S., Casey, B.J., 2009. Functional MRI and response inhibition in children exposed to cocaine in utero. Dev. Neurosci. 31, 159–166.
Sirnes, E., Oltedal, L., Bartsch, H., Eide, G.E., Elgen, I.B., Aukland, S.M., 2017. Brain morphology in school-aged children with prenatal opioid exposure: a structural MRI study. Early Hum. Dev. 106-107, 33–39.
Sirnes, E., Griffiths, S.T., Aukland, S.M., Eide, G.E., Elgen, I.B., Gundersen, H., 2018. Functional MRI in prenatally opioid-exposed children during a working memory-selective attention task. Neurotoxicol. Teratol. 66, 46–54.
Smith, A.M., Fried, P.A., Hogan, M.J., Cameron, I., 2004. Effects of prenatal marijuana on response inhibition: an fMRI study of young adults. Neurotoxicol. Teratol. 26, 533–542.
Smith, A.M., Fried, P.A., Hogan, M.J., Cameron, I., 2006a. Effects of prenatal marijuana on visuospatial working memory: an fMRI study in young adults. Neurotoxicol. Teratol. 28, 286–295.
Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., Behrens, T.E., 2006b. Tract-based spatial statistics: Vxelwise analysis of multi-subject diffusion data. Neuroimage 31, 1487–1505.
Smith, A.M., Mioduszewski, O., Hatchard, T., Byron-Alhassan, A., Fall, C., Fried, P.A., 2016. Prenatal marijuana exposure impacts executive functioning into young adulthood: an fMRI study. Neurotoxicol. Teratol. 58, 53–59.
Sowell, E.R., Thompson, P.M., Holmes, C.J., Batth, R., Jernigan, T.L., Toga, A.W., 1999. Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. Neuroimage 9, 587–597.
Sowell, E.R., Thompson, P.M., Leonard, C.M., Welcome, S.E., Kan, E., Toga, A.W., 2004. Longitudinal mapping of cortical thickness and brain growth in normal children. J. Neurosci. 24, 8223–8231.
Sussman, S., Arnett, J.J., 2014. Emerging adulthood: developmental period facilitative of the addictions. Eval. Health Prof. 37, 147–155.
Taylor, M.J., McCulloch, D.L., 1992. Visual evoked potentials in infants and children. J. Clin. Neurophysiol. 9, 357–372.
Thompson, B.L., Levitt, P., Stanwood, G.D., 2009. Prenatal exposure to drugs: effects on brain development and implications for policy and education. Nat. Rev. Neurosci. 10, 303–312.
Walhovd, K.B., Moe, V., Slinning, K., Due-Tonnessen, P., Bjornerud, A., Dale, A.M., van der Kouwe, A., Quinn, B.T., Kosofsky, B., Greve, D., Fischl, B., 2007. Volumetric cerebral characteristics of children exposed to opiates and other substances in utero. NeuroImage 36, 1331–1344.
Walhovd, K.B., Westlye, L.T., Moe, V., Slinning, K., Due-Tonnessen, P., Bjornerud, A., van der Kouwe, A., Dale, A.M., Fjell, A.M., 2010. White matter characteristics and cognition in prenatally opiate- and polysubstance-exposed children: a diffusion tensor imaging study. AJNR Am. J. Neuroradiol. 31, 894–900.
Walhovd, K.B., Watts, R., Amlien, I., Woodward, L.J., 2012. Neural tract development of infants born to methadone-maintained mothers. Pediatr. Neurol. 47, 1–6.
Warner, T.D., Behnke, M., Eyler, F.D., Padgett, K., Leonard, C., Hou, W., Garvan, C.W., Schmalfuss, I.M., Blackband, S.J., 2006. Diffusion tensor imaging of frontal white matter and executive functioning in cocaine-exposed children. Pediatrics 118, 2014–2024.
Wharton, F.L., Taylor, Paul A., Wharton, C.M.R., Molteno, C.D., Wintermark, P., Lindinger, N.M., 2018. Prenatal methamphetamine exposure is associated with corticostriatal white matter changes in neonates. Metab. Brain Dis. 33.
Whitham, J.N., Spurrier, N.J., Sawyer, M.G., Baghurst, P.A., Taplin, J.E., White, J.M., Gordon, A.L., 2010. The effects of prenatal exposure to buprenorphine or methadone on infant visual evoked potentials. Neurotoxicol. Teratol. 32, 280–288.
Whitham, J.N., Spurrier, N.J., Baghurst, P.A., Weston, P., Sawyer, M.G., 2015. Visual evoked potential latencies of three-year-old children prenatally exposed to buprenorphine or methadone compared with non-opioid exposed children: the results of a longitudinal study. Neurotoxicol. Teratol. 52, 17–24.
Willford, J.A., Singhabahu, D., Herat, A., Richardson, G.A., 2018. An examination of the association between prenatal cocaine exposure and brain activation measures of arousal and attention in young adults: an fMRI study using the attention network task. Neurotoxicol. Teratol. 69, 1–10.
Yip, S.W., Potenza, E.B., Balodis, I.M., Lacadie, C.M., Sinha, R., Mayes, L.C., Potenza, M.N., 2014a. Prenatal cocaine exposure and adolescent neural responses to appetitive and stressful stimuli. Neuropsychopharmacology 39, 2824–2834.
Yip, S.W., Potenza, E.B., Balodis, I.M., Lacadie, C.M., Sinha, R., Mayes, L.C., Potenza, M.N., 2014b. Prenatal cocaine exposure and adolescent neural responses to appetitive and stressful stimuli. Neuropsychopharmacology 39, 2824–2834.
Yip, S.W., Lacadie, C.M., Sinha, R., Mayes, L.C., Potenza, M.N., 2016. Prenatal cocaine exposure, illicit-substance use and stress and craving processes during adolescence. Drug Alcohol Depend. 158, 76–85.
Zakiniaeiz, Y., Yip, S.W., Balodis, I.M., Lacadie, C.M., Scheinost, D., Constable, R.T., Mayes, L.C., Sinha, R., Potenza, M.N., 2017. Altered functional connectivity to stressful stimuli in prenatally cocaine-exposed adolescents. Drug Alcohol Depend. 180, 129–136.