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Prenatal exposure to drugs: effects on brain development and implications for policy and education

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Abstract

The effects of prenatal exposure to drugs on brain development are complex and are modulated by the timing, dose, and route of drug exposure. It is difficult to assess these effects in clinical cohorts, which are beset with multiple exposures and difficulties in documenting use patterns. This can lead to misinterpretation of research findings by the general public, the media and policy makers, who may mistakenly assume that the legal or illegal status of a drug correlates with its biological impact on fetal brain development and long-term clinical outcomes. It is important to close the gap between what science tells us about the impact of prenatal drug exposure on the fetus and the mother, and what we do programmatically with regard to at-risk populations.

Introduction

Chemical neurotransmitters serve important functions in the coordination of the development of neurons and brain circuits (Box 1). Psychoactive drugs modulate receptors, transporters and other components of neurotransmission, many of which are expressed during prenatal stages of brain development, although their expression patterns and functions are sometimes quite different from their more typical roles later in life. Thus, the presence of these proteins in the developing brain underlies the well-documented impact of prenatal drug exposure on brain architecture, chemistry and neurobehavioral function in clinical cohorts and in animal models.

Many legal drugs such as nicotine and alcohol can produce more severe deficits on brain development than some illicit drugs such as cocaine. However, erroneous and biased interpretations of the scientific literature often affect educational programs and even legal proceedings. For example, a pregnant woman whose emergency room toxicology screen revealed cocaine use was recently jailed and accused of using a deadly weapon against her unborn child in Tennessee, United States [1]. Such policy decisions may have unintended adverse consequences: for example, they might harm the fetus due to pathophysiological activation of the maternal stress response system [2] and they might cause pregnant women addicted to drugs to avoid prenatal medical care (Box 2).

Research findings in humans and animal models should be used to inform better policy and program development to reduce the population of children who are exposed to drugs prenatally. Much of the human data is being generated by the National Children's Study, which aims to examine the effects of environmental influences on the health and development of 100,000

Further information
The National Children's Study http://www.nationalchildrensstudy.gov/
National Scientific Council on the Developing Child http://www.developingchild.net/
Translating time website http://www.translatingtime.net/
Frameworks Institute http://www.frameworksinstitute.org/sfa.html

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children across the United States. However, logistical issues have made it difficult to coordinate and retain participation of the mothers and children.

In this article, we describe findings from relevant animal models that illuminate the specific mechanisms by which drugs of abuse, both illegal and legal, act on the brain. It is not possible to adequately review all drugs and all models (see [3-6] for other relevant reviews), thus we have selected a few examples in which substantial data have been generated. We highlight clinical findings in humans that parallel many of the findings in model systems. Finally, we discuss the complex social and policy issues involved in providing appropriate support structures for children exposed to drugs *in utero* to help improve their neurodevelopmental trajectory.

Animal models of prenatal drug abuse

The utility of animal models for understanding typical and atypical human development is well established. Animal models have enabled us to begin to elucidate the complex neurodevelopmental consequences of prenatal drug exposure. Although basic behavior and some aspects of global structure and functional neural activity can be studied in humans exposed developmentally to drugs, the specific neuroanatomical, molecular, and cellular consequences underlying these behavioral changes are not accessible to study *in vivo*. Well-designed animal models can therefore be powerful tools for revealing the neurobiological alterations that underlie later disrupted behavior.

However, the challenges of developing appropriate animal models are substantial. For example, although the orderly assembly of the cellular elements that comprise the developing nervous system is highly conserved across vertebrate species, the timing and duration of histogenic events and maturation of neurotransmitter systems may differ substantially. Moreover, metabolic pathways differ based on routes of exposure and across species; this therefore represents another important variable in recapitulating drug exposure patterns in humans. There are several key experimental variables to be considered when designing an animal model of prenatal drug exposure: the species to be used, the age of the embryo during exposure, the frequency and duration of exposure, the route of administration and the drug concentration.

The timeline for neurodevelopmental milestones has been documented in humans and for most animals used as models (Figure 1) [7-9]. Thus, designing animal models of drug exposure during particular stages of fetal animal development that correlate with the timing of exposure during human pregnancy is realistic, at least to a first approximation. There are, however, further complications when considering how to model human exposure. These include both nutritional issues and the use of two or more drugs in combination. In addition, providing an environment in which the mother feels comfortable in disclosing the length of exposure, amount used and combinations of drugs used is critical for determining clinical profiles and in subsequently using the data to establish accurate animal models. Furthermore, some processes that occur during the third trimester of *in utero* development in humans occur postnatally in rodents and thus might be missed by studies conducted during gestation only. However, further complicating matters, rodent maternal and environmental interactions with the offspring are crucial for proper social and emotional development during this postnatal period, a situation that differs from that of humans during late gestation.

Different species may provide distinct advantages depending on the specific hypotheses to be tested. For example, if one wishes to investigate the roles of certain genes in mediating the impact of prenatal drug exposure, genetically engineered mice may be most advantageous. This advantage might be weighed against the difficulties in administering drugs repeatedly to pregnant mice. Self-administration drug paradigms during pregnancy may be more imitative of human abuse than experimenter administered paradigms and rats have been the primary

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model species for this approach. On the other hand, establishing self-administration in rodents is sometimes problematic and requires other reinforcers to be superimposed on drug administration. Non-human primates most closely model the temporal domains of human brain development and behavior. However, it is logistically far more difficult and expensive to use non-human primates for research purposes, and as such this is not the ideal approach for rapid mechanistic discoveries. The long history of animal model research has in fact employed many different models and comparison of fundamental discoveries across species has been difficult. Cautious interpretation, in which one attempts to identify convergent findings, is particularly necessary for further advancements in the field. Convergence is often found in translating across larger behavioral dimensions, rather than in detailed features of the models.

Lastly, patterns of administration of different drugs vary. Some drugs (such as cocaine) are typically used in discrete episodes, whereas others (such as nicotine and alcohol) tend to be used chronically. This issue is likely to be important in determining the effects of developmental drug exposures. Thus, the effects of various substances may be reflective of both their inherent neurotoxicity and also of the patterns with which they are (ab)used.

Effects of illegal drugs of abuse

Cocaine

Cocaine is a psychostimulant that binds to monoaminergic – preferably dopaminergic – transporters and prevents uptake of extracellular monamines into the pre-synaptic cell, resulting in excess neurotransmitter in the synaptic cleft and excess stimulation of dopamine receptors. There are five known dopamine receptors: D1-like receptors (D1 and D5), and D2-like receptors (D2, D3, and D4). The roles of dopamine and these receptors in reward pathways have been demonstrated in both human and animal model [10, 11]. Dopamine receptors are also located in the prefrontal cortex, hypothalamus, brainstem and even outside the CNS [12-15]. The dopamine system develops early in gestation in all vertebrate species, and might therefore be sensitive to exogenous manipulation early in gestation. In fact, some early reports suggested a very severe phenotype in children exposed to cocaine *in utero* [16-18]. Children were thought to be emotionally disrupted, cognitively impaired, less likely to socially interact, and more likely to die from sudden infant death syndrome (SIDS). Thus, the term "crack-baby" was introduced to describe children exposed to cocaine prenatally. However, these original studies were confounded by very small sample sizes, polydrug use, nutritional status and other psychosocial problems.

We now know that, irrespective of species, the extent to which prenatal exposure to cocaine affects brain development varies significantly. The assumptions made by the public about the biological impact of prenatal cocaine exposure may be based on the severity of symptoms associated with cocaine addiction, and the illegal nature of the substance. In humans, longitudinal studies have shown that there are long-term consequences of prenatal cocaine exposure; however, the behavioral dysfunction appears to be mild [19-24]. The recreational use of cocaine during pregnancy results in a subtle, though dominant developmental phenotype that resembles attention deficit disorder (ADHD) [19-22, 25-29]. Detailed studies have demonstrated that prenatal cocaine exposure can have long-lasting negative effects on cognitive and attention systems, mediated via regions such as the prefrontal cortex, and other higher-order cortical areas that express dopamine receptors and receive rich dopaminergic projections from the midbrain (Table 1) [19, 24, 27, 30-32]. Recent data also suggest that there is increased likelihood that children exposed to cocaine prenatally will require special needs programs [33], which, from both an individual and societal perspective, is expensive.

Animal models confirm that prenatal cocaine exposure results in specific permanent behavioral, cellular, and molecular changes [34-37]. An intravenous model of prenatal cocaine

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exposure in the rabbit closely models the pharmacokinetic profile of human abusers [38-40]. It has been used to delineate a number of highly specific changes, including altered GABA content in the cortex, altered calcium binding protein expression, morphological changes in pyramidal cells, and decreased dopamine D_1 receptor coupling to its cognate G-protein, $G_{s\alpha}$ [41-46] (Table 1). The most surprising alteration was a permanent reduction in second messenger coupling, which was found to be due to abnormal internalization of the D_1 receptor. This suggested that the D_1 receptor is not trafficked properly to the cell membrane where it would then interact with $G_{s\alpha}$ [47]. These cellular and molecular findings were observed only in dopamine rich cortical areas, which are intimately involved in cognition and executive functioning tasks, including attention [48-53]. These studies have also been able to directly relate the timing of *in utero* cocaine exposure to its deleterious effects in offspring and suggest that the second trimester may be a particularly vulnerable period [54].

Other animal models show that prenatal cocaine exposure alters basic processes of neocortical development, including cell production and migration [55-60]. These findings are consistent with recent studies demonstrating that dopamine can regulate progenitor cell proliferation and neuronal migration during prenatal development [61, 62].

Behavioral changes have been reported in various animal models, including deficits in attention tasks, emotional reactivity, and the reinforcing properties of drugs of abuse [30-32, 63, 64]. These findings correspond with the human clinical literature that reports disturbances in both attention and emotion regulation in children exposed prenatally to cocaine.

Amphetamine/Methamphetamine

Amphetamine and methamphetamine are also psychostimulants; however, they target the monoaminergic system in a mechanistically distinct fashion from cocaine. Both drugs reverse the actions of monoamine transporters and enhance release of dopamine, norepinephrine, and serotonin into the synaptic cleft, increasing their availability to act upon post-synaptic receptors. In addition, both drugs can block the re-uptake and degradation of these neurotransmitters, further increasing their concentrations in the synaptic cleft. The addition of a methyl group allows methamphetamine to move through lipid permeable membranes easily. Both amphetamine and methamphetamine are routinely ingested, snorted, and smoked. The frequency of use and abuse of amphetamine and methamphetamine has steadfastly risen in the human population, exceeding cocaine use in many regions of the United States [65].

Because methamphetamine and amphetamine use during pregnancy has become prolific only recently, there are few studies defining its long-term consequences. Children exposed to methamphetamine or amphetamine during prenatal development show decreased arousal, increased stress, decreased school achievements, movement disturbances and low birth weight (a high risk factor for special needs programs at school age) [66-70]. Neurocognitive testing showed that these children score lower on sustained attention, long-term spatial and verbal memory, and visual motor integration [71]. Neuroimaging has produced reports of smaller striatum and hippocampus volumes and decreased numbers of dopamine D_2 receptors and dopamine transporter density [71, 72]. Polydrug use and other psychosocial risks complicate these studies [70, 73], making it challenging to define the clinical impact of each drug individually. Animal models have helped delineate the specific neurodevelopmental consequences of prenatal amphetamine and methamphetamine exposure.

The neurobiological consequences of prenatal methamphetamine and amphetamine exposure have been studied in mice and rats. Animals exposed to methamphetamine have lower birth weights, increased incidence of microgyria (smaller and more numerous convolutions in the cerebral cortex than usual), and deficits in visual system development [74-76]. They also display impaired postural motor movements, deficits in specific learning paradigms, increased startle

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reflexes and decreased pre-pulse inhibition [76, 77]. Furthermore, alterations in the levels and activity of the noradrenergic and serotonergic systems have been demonstrated in animals exposed to either amphetamine or methamphetamine [78-80]. Some of the functional consequences (such as impaired sensory-motor coordination) of prenatal methamphetamine exposure are transmitted to the next generation of offspring [81]. These findings demonstrate that prenatal amphetamine or methamphetamine exposure leads to a complex behavioral phenotype with similarly complex molecular and cellular roots.

Effects of Legal Drugs of Abuse

Nicotine

Nicotine binds to nicotinic acetylcholine receptors (nAChRs), a class of ligand-gated ion channels that are widely expressed throughout the fetal nervous system. Nicotine is usually presented to the fetus through maternal smoking or environmental exposure to second-hand smoke. Research has provided unequivocal evidence that active smoking and passive exposure to second-hand smoke can be teratogenic (for review, see [82]), can lead to decreased birth weight and can increase the risks of preterm birth and SIDS (Table 1), all of which are high risk factors for behavioral impairment [69, 83-85]. Numerous studies support a robust relationship between developmental tobacco smoke exposure and attention deficit disorders, hyperactivity, antisocial behavior and learning disabilities [86-94]. However, differences in the amount of nicotine and other chemicals in different tobacco products make it challenging to compare findings across ethnic or age groups. Furthermore, the presence of additional potential neurotoxicants and biomodulators in tobacco smoke, make it difficult to determine the specific effects of nicotine exposure. This presents a challenge for clinicians who may wish to recommend nicotine replacement therapy (NRT) to pregnant patients who have difficulty terminating smoking. Although the additional chemicals are absent in NRT, high amounts of nicotine are still presented to the fetus. Based on animal studies (see below), such exposure is likely to lead to long-term disruption of brain architecture and chemistry. In fact, transdermal patch NRT may actually worsen birth outcomes relative to active smoking [95, 96]. One possibility as reviewed recently [97, 98], is that this may reflect the continuous-delivery provided by the patch, which in animal models has been shown to increase fetal brain nicotine levels up to three times maternal blood levels [99].

Animal studies have provided the most compelling evidence that nicotine has substantial negative neurodevelopmental impact. Activation of nAChRs affects morphogenesis, spontaneous neural activity, and neuronal survival in rodents [100]. In animals, plasma nicotine levels similar to those of pregnant women smoking "moderate" numbers of cigarettes produce potent neurobehavioral effects – including changes in locomotor activity, reward systems, anxiety, and cognition – in offspring [101, 102,100, 103-105]. Higher doses produce fetal hypoxia and substantial growth retardation [106]. Cortical cholinergic systems modulate sensory cognitive processing [107], and prenatal nicotine exposure impairs cognitive functions in animal models and in children [100, 108]. Intriguingly, nicotine inhibits aromatase, an enzyme involved in estrogen synthesis in the placenta [109]; this may interfere with sexual differentiation of the brain in males and changes have been observed in the timing of puberty onset in gestationally exposed male adolescents [110]. Based on these findings, reducing smoking by pregnant women and their immediate family members will be very beneficial; whereas the value of NRT in pregnant women is questionable and requires in depth evaluation through prospective studies [98].

Alcohol

Alcohol use spans all socioeconomic classes, gender, race, education, and cultural groups. It is a pharmacological depressant, blocking NMDA receptor activity and increasing GABAergic

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activity, thereby decreasing cortical and sub-cortical activity [111, 112]. Alcohol can also disrupt growth factor receptor signaling by disrupting plasma membrane integrity [113, 114]. GABA and its receptors are present early in neuronal development, and can modulate progenitor cell proliferation, cell migration and neurite growth [115-117]. Alcohol crosses the placental barrier at any point during pregnancy and thus can severely impact numerous histogenic processes (see below and Table 1).

There is overwhelming basic and clinical evidence regarding the negative neurodevelopmental consequences of prenatal alcohol exposure. These comprise an ICD/DSM recognized disorder, fetal alcohol syndrome, characterized by growth deficiencies, craniofacial dysmorphologies, and CNS damage [3, 118-121]. Prenatal alcohol exposure can cause intellectual disability, deficits in learning, attention and motor development and hyperactivity [119, 120, 122-125]. Although concomitant use of other drugs with alcohol is not unusual, alcohol is often used as a solitary drug. This clinical population provides a less mechanistically complex picture of the neurodevelopmental consequences of prenatal alcohol exposure. In addition, animal models have provided further understanding of the cellular and molecular consequences of prenatal ethanol exposure.

Animal models of prenatal ethanol exposure have confirmed an increase in birth defects including neurological dysfunction [3, 126-130]. Exposure during all gestational periods has dramatic teratogenic consequences [131-133]. There are reports of a decrease in spinal and cranial motor neuron production and size, neocortical and hippocampal dysgenesis, increased neuronal cell death, reduced or delayed neuronal migration and a decrease in myelination [134-137]. Ethanol exposure also disrupts the integrity of plasma membrane receptors [138, 139]. Thus, in addition to direct antagonism of neurotransmitter receptors, receptor tyrosine kinase signaling is also disrupted, leading to altered neurotrophic factor modulation of multiple histogenic events.

Elegant studies have begun to prove the impact of prenatal alcohol on endocrine function [140, 141]. As well as alcohol's direct effects on the fetus, it also acts directly on the hypothalamic-pituitary-adrenal (HPA) axis of both the fetus and the mother. Modulating the HPA axis during development can permanently alter its responsiveness to later stressors, setting off a cascade of behavioral, cognitive, and cellular alterations in the adult [142]. Similarly, alterations in maternal HPA activity could underlie some of the long-lasting consequences following prenatal alcohol. As such, intervention and behavioral therapy for these children might consider methods used in clinical populations of children exposed to severe stress *in utero*.

Effects of Prescription Neurotherapeutics

Antidepressant Medications

A report of a higher rate of cardiac abnormalities in the children of women using selective serotonin reuptake inhibitors (SSRIs) during pregnancy [143, 144] has led to enormous public and scientific interest. Animal studies have long implicated serotonin, the target of many antidepressants, in the development of the brain and peripheral organs [145-147]. Serotonin and its receptors are expressed in the brain early in prenatal development [12, 148-151], and can modify dendritic and axonal differentiation [149, 152] (Figure 1). Although the mechanism remains unknown, early postnatal disruption of serotonin signaling in the rodent (at stages roughly equivalent to 3rd trimester and neonatal human periods), can permanently increase anxiety behaviors and disrupt learning [153, 154].

The animal studies are compelling, but epidemiological studies to date do not provide evidence of an increased risk of birth defects following SSRI use during pregnancy [155-159]. It is important to consider that even though the rate of overt birth defects compared to the general population

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does not increase at typical dose levels, subtle yet significant behavioral dysfunctions in offspring could occur similar to prenatal cocaine exposure. The issues are thus complex and require additional, detailed studies to inform medical decisions. Health care professionals must weigh the relative neurodevelopmental impact of drug treatment of a psychiatric disorder against the potentially negative outcomes from untreated illnesses (including increased maternal stress due to depression or untreated neurochemical imbalances). Thus, when behavioral therapy alone is not effective in treating depression in a pregnant woman, the potential risk of drug therapy must be weighed against the risk for relapse of the disorder if pharmacological therapy is interrupted.

Other Prescription Medications

Several prescription medications are used for treatment of psychiatric, neurological and maternal pregnancy disorders. Little research has examined the long-term functional implications of these drug treatments, but new studies are beginning to highlight a complex clinical picture.

Concerns have been raised regarding the effects of antipsychotic medications (potent antagonists of dopamine and serotonin receptors) during pregnancy. Animal studies point to serious potential neurodevelopmental risks [160-164]. However, there have been few clinical studies [165, 166], making it difficult to draw accurate conclusions regarding long-term impact on fetal development. As with other psychoactive drugs, an individualized calculation of relative risk is very important to balance the potential risk of drug exposure against the risk of a potential psychotic episode if pharmacotherapy is suspended.

Another commonly prescribed drug is valproate, an anti-convulsant and anti-mania therapeutic which blocks voltage-gated sodium and T-type calcium channels and inhibits the transamination of GABA [167]. As a histone deacetylase inhibitor, valproate also can regulate the epigenetic modulation of gene transcription [168]. Clinical data demonstrates high risk for autism spectrum disorder (ASD), teratogenic (neural tube defects; cranio-facial dysmorphia) and neurotoxic (apoptosis, reduced cell proliferation in multiple brain areas) effects of valproate exposure [169, 170]. Rats exposed prenatally have lower sensitivity to pain, increased repetitive/stereotypic-like activity, higher anxiety, decreased level of social interaction and an increased basal level of corticosterone [171, 172]. Alterations in NMDA receptor expression, enhanced long-term potentiation and neocortical hyperconnectivity also have been reported [173, 174].

Terbutaline and other related drugs were previously used commonly in late term pregnancies to reduce premature uterine contractions via stimulation of the β_2-adrenergic receptor [175]. Terbutaline exposure to neonatal animals results in neuroinflammation and long-lasting behavioral and cellular deficits [176-178]. Furthermore, children exposed to terbutaline or related adrenoceptor stimulants during late gestation may have an increased incidence of learning and neuropsychiatric disorders [179, 180]. Recent clinical studies have revealed an increased risk for the development of ASD in exposed offspring, consistent with a report of a modest increase in risk due to an allelic variant in the gene encoding the β_2-adrenergic receptor [181]; whether this genetic predisposition and environmental risk interact with one another is not yet known. In fact, the efficacy of these drugs in preventing preterm delivery when used for maintenance tocolysis is suspect [182], and their recognition for such uses has been withdrawn.

Balancing Prenatal Drug Exposure

Basic and clinical research unequivocally demonstrates that recreational or prescription use of drugs during pregnancy can be viewed as an anathema to healthy development. There is a clear conundrum, however, with regard to the need to balance exposure (in a clinically prescribed

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population) versus non-exposure when considering the long-term functional impact on brain development. The difficulties relate to the fact that high prenatal stress, malnutrition and untreated maternal psychiatric disorders can themselves increase risk for developmental disabilities in children.

With regard to recreational drugs, human addictive behavior makes this issue far more complicated than a simple public policy approach of 'just say no'. Furthermore, it is clear that the idea that illegal drugs are more harmful to the unborn fetus than legal drugs is a misnomer; this concept, which strongly influences public policy, is not supported by findings from carefully designed and controlled research studies. For pregnant women who abuse drugs prior to conception, withdrawal of these drugs post-conception is not without risk to the fetus. Maternal stress can be severe during withdrawal, and general health status may decline; both severely impacting brain development of the fetus.

We now realize that prescription drug treatments for pregnant women with psychiatric and neurological disorders can have negative effects on fetal brain development and long-term behavioral outcomes. However, the underlying maternal pathophysiology of untreated disorders can lead to high risk nutritional and stress status for both the mother and the fetus. Perhaps underscoring the level of complexity of the maternal-fetal relationship, balancing these issues makes formulation of public and medical policies less straightforward and far more difficult than generally appreciated.

Proposals to Reduce Bias

When considering particular conditions or states, people generally default to frames that are most familiar to them. Frames are principles that are socially shared and persistent over time and which work symbolically to meaningfully structure the social world [183]. It is essential for scientists to understand this concept, because the inadequate communication of information causes people to default to these frames. Framing has been defined as the process of selecting a few elements of a perceived reality and assembling a narrative that highlights connections among them to promote a particular interpretation for an individual [184]. We have already mentioned the misnomers that illustrate this concept. The term 'crack baby' evolved from social perceptions regarding individuals who use crack cocaine, the assumed severity of impact of fetal exposure to an illegal drug, and a lack of understanding of the complex maternal status that included polydrug use and malnutrition. The press and scientists alike were culpable in promoting this image in the absence of documented biological and behavioral impact. By the time science caught up, the frame had been cemented, and remains an influential factor in defining public policy (Box 2).

Fully developed frames perform four functions: problem definition, causal analysis, moral judgment, and remedy promotion [184, 185]. In order to provide more accurate information for policy makers the original concept must be reframed. Initially, the science must be explained in such a way that it redirects attention away from the default positions. In part, redefining frames involves identifying values and explanations that make the societal, not individual, goals, obvious. This can be done best by creating and subsequently using simplifying models to explain brain development, which in turn will assist in explaining the impact of drugs and stressors on the process. This provides an opportunity for science to explain how current policies surrounding drug use may have even more negative effects on the fetus than the drug itself, under certain circumstances. These models thus become vehicles through which science can positively influence policy thinking and decisions.

The Frameworks Institute has developed a metaphorical frame of brain development that captures the essence of the scientific concept [186]. According to this model, the early years of life matter because early experiences affect the architecture of the maturing brain. The quality

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of that architecture establishes either a sturdy or a fragile foundation for the development and behavior that follows. Therefore, similar to building a house, getting things right the first time is easier than trying to fix them later [187]. This explanation of brain development reduces the complexity of the problem to a simple, concrete analogy that helps policymakers, members of the media and the public organize information into a clear picture. Thus, understanding that the assembly of brain architecture starts early, from the bottom up, paralleling the process of skill development in a child makes the connection between the time dependent relationship between structure and function. This facilitates, and stimulates interest in understanding factors that can influence the process. For example, discussions of the more potent influence of alcohol and nicotine on developing brain architecture, compared to cocaine leads directly to the conclusion that such exposures also must have more profound functional consequences. This reduces the impact of the default frame (that illegal drugs are more detrimental to fetal development than legal drugs). Likewise, explanations of the impact of 'toxic stress', such as severe malnutrition, drug exposure, poor healthcare or lengthy incarceration, on fetal brain architecture can lead to discussions between scientists and policy makers that evaluate the factors that may have the greatest impact on child development [187] (Box 3). There is thus an attainable goal of eliminating default frames and introducing more scientifically-based simplifying models that can alter the course of social and legal policies to best manage the difficulties of drug exposure during pregnancy (Box 3).

Looking to the future

Scientists often find it bewildering that what appear to be basic concepts of development are misrepresented or misinterpreted when policy decisions are being made. Policies are then established that are not based on the scientifically recognized factors that regulate development. Instead, policies reflect default frames of child development that typically focus on family, individual responsibility and safety - illegal equals 'more dangerous'; legal equals 'less dangerous'. Moreover, experts may unwittingly cross the line from information-providers to advocates. Science experts could thus be viewed as biased responders to queries from policy-makers, moving beyond their perceived area of expertise. Scientific findings need to be shared with the community in such a way that we avoid loading information into default frames so that science can inform the way that we, and other members of society, think about problems.

There are still significant questions that will require additional investigations. For example, what are the consequences on fetal brain development of suspending drug treatment of a psychiatric disorder in a pregnant woman? Are there sensitive and critical periods of fetal brain development that are more or less vulnerable to exposures of specific agents? Can we better define the biological interactions of multiple drug exposures, nutritional status and maternal stress that influence fetal brain development? Creating simple developmental models that clearly communicate these influences will be essential. Such models will assist policy makers in developing sound strategies for reducing the incidence of drug exposure during pregnancy and for implementing more effective treatments that maximize healthy development of the fetus, when drug exposure during pregnancy does occur.

Box 1

Effects of neurotransmitters on brain development

Studies beginning almost 50 years ago demonstrated that the capacity to synthesize and degrade neurotransmitters, particularly biogenic amines, many of the receptors through which they signal, and circuits that utilized them emerged early in embryogenesis [100, 146, 188-192]. Given the appearance of neurotransmitters well before synapse formation, a variety of roles in neurodevelopmental processes were postulated, but not demonstrated. Modern *in vitro* approaches and genetic engineering of mice has facilitated discoveries that identify

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the pleiotropic nature of neurotransmitter signaling in neurodevelopmental processes. As a few examples of non-synaptic functions, dopamine regulates progenitor cell cycle kinetics and dendritic growth [62, 193], serotonin modulates cell proliferation and the response of growing axons to classic guidance molecules [149, 194], GABA activates the migration of developing neurons [195], and glutamate regulates oligodendrocyte precursor survival [196]. Key to these influences is the expression of subsets of receptors in transient developmental patterns that mediate early neurotransmitter signaling for developmental purposes. This is followed by spatial and temporal reorganization and the expression of other subtypes that may be involved in modulating or directly inducing synaptic transmission.

Box 2

Criminal prosecution of pregnant women using drugs of abuse

A study in 1985 reporting damaging effects of cocaine use during pregnancy [16] produced a massive media response. Based on the media reports, laws were enacted in the United States requiring health care professionals to report pregnant illicit drug users to child welfare authorities and legislation was pursued to make drug use during pregnancy a criminal offense. The desire to guard fetal health and outcomes is understandable; however, research shows that pregnant women who fear prosecution and the potential loss of their children as a result of using drugs of abuse are less likely to seek essential prenatal and medical care. Thus, the policies that were meant to deter illegal drug use among pregnant women had unintended consequences, resulting in even greater risk to the fetus [197, 198]. Moreover, the threat of criminal punishment can foster fear and mistrust between doctors and their patients, increase maternal stress, and endanger the health of women and their future children. Based on the science, one could argue that this is considerably worse than the drug exposure itself.

South Carolina in the United States has been particularly aggressive in using the court system in an attempt to deter drug use during pregnancy. At least 90 women have been prosecuted for stillbirths after using drugs or alcohol. Between 1989 and 1994, a prominent hospital in Charlēston adopted a policy of informing police of any positive test for cocaine in pregnant women. The patients were informed that an arrest would occur if they failed to successfully complete a drug program. If a positive test was obtained at delivery the woman would be immediately arrested and charged [199]. This policy was discontinued in 1994 because of pressures applied by the Department of Health and Human Services [199], and was found to be constitutionally deficient in 2001 by the Supreme Court [200].

In May 2008, the South Carolina Supreme Court overthrew the homicide by child abuse conviction of one of these women, Regina McKnight [201]. They ruled that Mrs. McKnight had not received a fair trial due to ineffective counsel and the inclusion of unsupported scientific evidence [201]. It is not yet known whether she will be re-tried for the charge, but these events suggest that policy may be coming into better accordance with scientific data.

Box 3

Closing the gap – Using what we know to inform what we do

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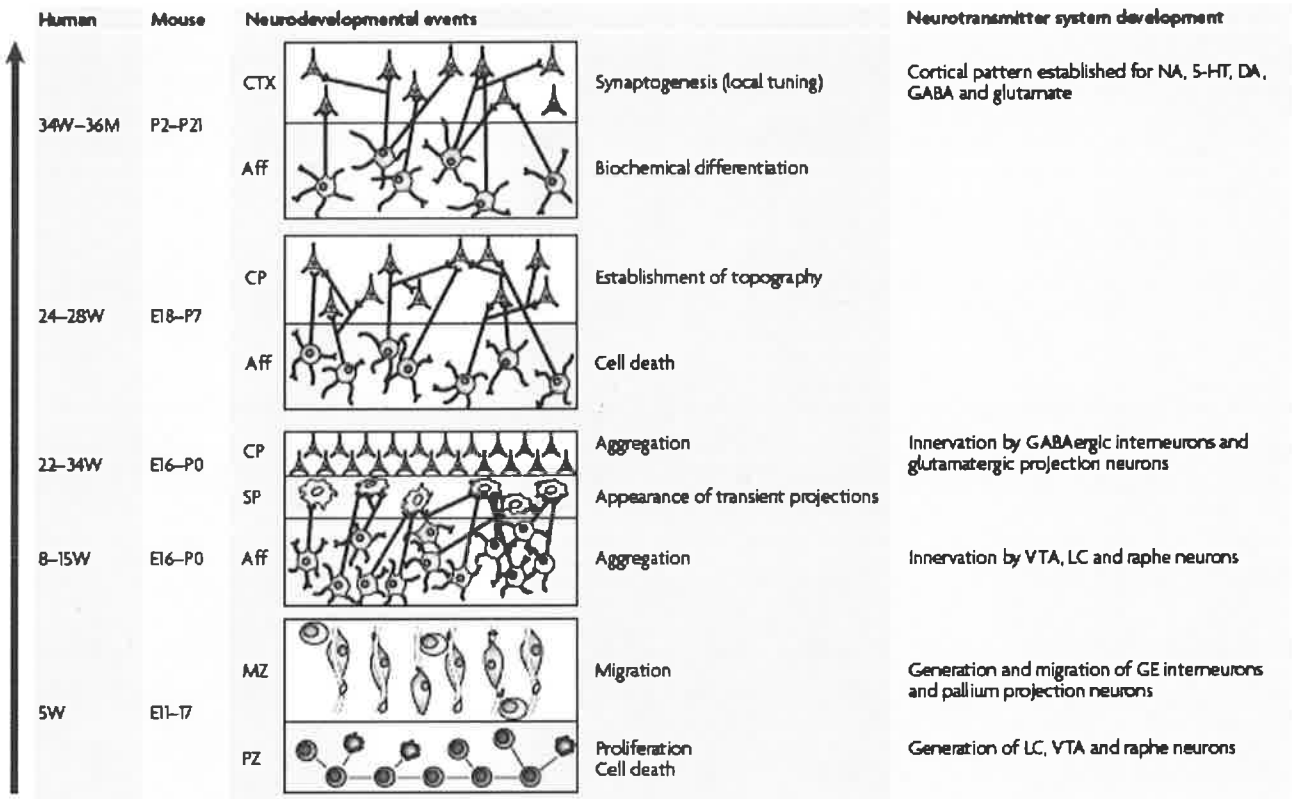

Figure 1. Developmental Events and Ontogeny of Drug Targets

The peak periods of key neurodevelopmental events are depicted. Reference to timing of neurotransmitter system development includes appearance of receptors, transporters and synthetic machinery. Note that some of these neurotransmitter elements may continue to mature through puberty. Gestational age for both human (black font) and mouse (red font) are aligned with the black arrow to define the timeline for these events. Emerging drug targets (receptors, transporters, etc) are depicted along this same timeline in purple. Aff, afferents; CP, cortical plate; CTX, cortex; DA, dopamine; E, embryonic; GE, ganglionic eminence; LC, locus coeruleus; M, months; MZ, marginal zone; P, postnatal; PZ, proliferative zone; SP, sub-plate; VTA, ventral tegmental area; W, weeks; 5-HT, serotonin. Adapted from [202, 203].

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Factors that Influence Policy Decisions	Maternal Drug Abuse Policies Strategies to Affect Public Policy
• Public / Media Perception *(free will; legality; excesses)* • What Science Tells Us *(maternal health; fetal-maternal interactions; brain architecture and chemistry)* • Policy Makers *(public perception; legality; child welfare)*	• Develop simplifying frames of factors that impact child development *(e.g. drugs, stress, nutrition)* • Develop key working partnerships *(National Conference of State Legislatures; childhood-focused private foundations)* • Engage scientists in providing impartial testimony. (*"What science tells us", "Just the facts"*) • Scientists work with video and print media to tell a core story of the impact of drugs of abuse on fetal development.

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Table 1

Neurodevelopmental consequences of prenatal drug exposure.

Age of exposure	Drug	Neurochemistry involved	Neurodevelopmental consequences	References
Late early to mid gestation (primarily based on animal studies)	Cocaine	DA > NE and 5-HT Blocks monoaminergic transporters and Increases synaptic concentrations of monoamines	Altered neuroanatomical morphology, disrupted cognition, altered cellular signaling	18-37, 42-47, 54-59, 63-65, 203
Throughout gestation	Alcohol	GABA and NMDA Blocks NMDA receptor activity and increases GABAergic activity	Craniofacial dysmorphologies, decreased birth weight, hyperactivity, cognitive deficits, cortical dysgenesis, cell death, reduced brain volume	113-115, 118-120, 126-132
Throughout gestation	Nicotine	Acetylcholine Activates nAChRs	Decreased birth weight, hyperactivity, cognitive disabilities, emotional disruptions	82, 86-94, 96-98, 100-105, 107, 108
Throughout gestation and early postnatal exposure	Amphetamine/ Methamphetamine	DA > NE and 5-HT Reverses the action of monoaminergic transporters and Increases synaptic concentrations of monoamines	Low birth weight, decreased arousal, deficits in learning, decreased volume of hippocampus and striatum	66, 67, 70-73, 76-81