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Multigenerational and transgenerational effects of paternal exposure to drugs of abuse on behavioral and neural function

Lisa R. Goldberg, **Thomas J. Gould**

Department of Biobehavioral Health, Penn State University, 219 Biobehavioral Health Building, University Park, PA 16801, USA

Abstract

Addictions are highly heritable disorders, with heritability estimates ranging from 39% to 72%. Multiple studies suggest a link between paternal drug abuse and addiction in their children. However, patterns of inheritance cannot be explained purely by Mendelian genetic mechanisms. Exposure to drugs of abuse results in epigenetic changes that may be passed on through the germline. This mechanism of epigenetic transgenerational inheritance may provide a link between paternal drug exposure and addiction susceptibility in the offspring. Recent studies have begun to investigate the effect of paternal drug exposure on behavioral and neurobiological phenotypes in offspring of drug-exposed fathers in rodent models. This review aims to discuss behavioral and neural effects of paternal exposure to alcohol, cocaine, opioids, and nicotine. Although a special focus will be on addiction-relevant behaviors, additional behavioral effects including cognition, anxiety, and depressive-like behaviors will be discussed.

Keywords

addiction; alcohol; cocaine; epigenetics; nicotine; opioid

Introduction

Addiction is a result of a complex interaction between genetic, environmental, and drug use factors (Ducci & Goldman, 2012). It is clear from twin, family, and adoption studies that there is a major genetic component in alcohol, nicotine, cannabis, psychostimulant, and opioid abuse (Ducci & Goldman, 2012), with heritability estimates ranging from 0.39 to 0.72 (Ho *et al.*, 2010). Human genome-wide association studies of substance use disorders have identified numerous candidate loci and genes (Ho *et al.*, 2010; Ducci & Goldman, 2012; Jensen, 2016). However, these associated variants typically only account for a small fraction of the total heritability estimates, a phenomenon known as “missing heritability”

Correspondence: T. J. Gould, as above. tug70@psu.edu.

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Competing Interests

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(Eichler *et al.*, 2010). Although this "missing heritability" may be due in part to technical and experimental limitations, it is also possible that alternative biological mechanisms may mediate and explain this phenomenon. Additionally, human studies have found that the patterns of inheritance of drug use and abuse cannot be explained solely by simple genetic mechanisms (Schuckit *et al.*, 1972; Cloninger *et al.*, 1981).

Environmental factors, such as stress, play a key role in the development of substance use disorders, making drug addiction an archetypal gene by environment disorder. Therefore, both genetic and environmental factors contribute to an individual's susceptibility to addiction following initial exposure to drugs of abuse. Epigenetics can be viewed as the link between the environment and an individual's genome. Broadly, epigenetics is defined as alterations in gene expression without changes in DNA sequence (Jaenisch & Bird, 2003; Bird, 2007). Epigenetic changes are molecular modifications to both DNA and chromatin, including DNA methylation, histone post-translational modifications, and regulation by small non-coding RNAs (Li, 2002; Klose & Bird, 2006; Richards, 2006; Talbert & Henikoff, 2006).

Exposure to drugs of abuse results in epigenetic modifications that can mediate long-lasting neurobiological and behavioral changes (Nestler, 2014). For example, acute exposure to cocaine results in increased histone acetylation in the nucleus accumbens, and alternatively, treatment with a histone deacetylase inhibitor results in increased cocaine conditioned place preference (Kumar *et al.*, 2005). This study, and many others, have provided key evidence for a link between drug exposure, epigenetic modification and drug-induced behaviors in the drug-exposed individual. Beyond epigenetic modifications in brain regions pertinent to drug use, drug exposure may also result in epigenetic modifications in the sperm or ova (Vassoler & Sadri-Vakili, 2014). For example, histone modifications in the sperm are altered following cocaine self-administration (Vassoler *et al.*, 2013). Until recently, it was believed that epigenetic modifications were erased and not passed on to subsequent generations. However, epigenetic modifications, including DNA methylation, histone post-translational modifications, and non-coding RNAs, acquired in one generation can be inherited in the next generation (Bird, 2007; Manolio *et al.*, 2009; Skinner & Guerrero-Bosagna, 2009). For example, exposure to environmental toxins and pesticides can result in DNA methylation changes in sperm of subsequent generations (Guerrero-Bosagna *et al.*, 2010; Manikkam *et al.*, 2012a,b,c). Recently, it has been demonstrated that these epigenetic factors can contribute to disease heritability (Jirtle & Skinner, 2007; Skinner *et al.*, 2010) and may provide a link between environmental exposures and genetic inheritance, and ultimately explain the "missing heritability" phenomenon. The ability of environmental factors to promote the epigenetic transgenerational inheritance of disease and phenotypic variation has now been established in a number of organisms ranging from plants to humans, with a variety of environmental exposures (Skinner *et al.*, 2010). Therefore, it is possible that epigenetic modifications due to drug use may result in behavioral and neurobiological changes, and ultimately contribute to drug use and dependence across generations (Hughes, 2014).

Developmental neurobehavioral effects associated with prenatal drug exposure due to maternal drug use are well-characterized for some abused substances (Malanga & Kosofsky,

2003; Lester *et al.*, 2004; Ornoy & Ergaz, 2010; Sithisarn *et al.*, 2012). For example, a significant body of literature describes the effects of prenatal ethanol exposure on the brain (Swayze *et al.*, 1997), such as alterations in the development of the basal ganglia (Mattson *et al.*, 1996) and corpus callosum (Riley *et al.*, 1995). The effects of direct prenatal exposure are clear; however, less is known about the effects of parental drug use that does not result in direct exposure. Interestingly, multiple studies suggest a link between paternal alcohol abuse and alcohol abuse in their children (Ervin *et al.*, 1984; Peterson & Pihl, 1990; Pihl *et al.*, 1990; Ozkaragoz *et al.*, 1997), but genetic factors cannot completely explain the pattern of inheritance (Schuckit *et al.*, 1972; Cloninger *et al.*, 1981). Therefore, it is of interest to understand the effects of paternal drug exposure prior to conception on offspring neurobiology and addiction-relevant phenotypes. A focus on paternal transmission eliminates the consequences of direct *in utero* drug exposure and the potential influence of previous drug exposure in dams on maternal behavior. Drug exposure prior to conception, even as young as adolescence, can affect maternal care of pups in adulthood (Johnson *et al.*, 2011). Even a single episode of maternal separation can result in alterations in drug intake in the pups (Martini & Valverde, 2012). Therefore, investigating the offspring of a drug-exposed sire mated with a drug-naïve dam removes a potential confounding effect of maternal care irregularities. Although it is possible that interaction with a drug-exposed male may impact maternal rearing behaviors, recent studies examined maternal behaviors and found no differences between the dams bred with cocaine-exposed sires relative to control sires (Vassoler *et al.*, 2013), and between morphine-exposed sires relative to control sires (Li *et al.*, 2014).

Recent studies have begun to investigate the effect of paternal drug exposure on neurobiological and behavioral phenotypes of future generations. This review aims to summarize findings regarding the multigenerational and transgenerational inheritance of behavioral and neurobiological phenotypes in offspring of drug-exposed fathers. Special attention will be paid to studies addressing paternal exposure to alcohol, cocaine, opioids, and nicotine in animal models. THC or cannabinoid exposure studies will not be discussed because, to our knowledge, current studies include either only maternal exposure or both paternal and maternal exposure (Szutorisz *et al.*, 2014, 2016; Watson *et al.*, 2015), which does not allow for the dissociation of paternal and maternal exposure effects.

Notably, a clear distinction must be made between multigenerational and transgenerational inheritance when considering transmission of epigenetic effects. Transgenerational inheritance consists of germ-line-mediated inheritance of epigenetic information between generations in the absence of direct environmental influences that leads to phenotypic variation (Skinner, 2011). If an F0 father is exposed to a drug of abuse prior to mating, the germ cells that go on to produce the F1 generation are considered “exposed” and a phenotype in the F1 generation would represent multigeneraional inheritance. (Skinner, 2008, 2011). However, if the F1 generation is then never exposed to a drug of abuse, its offspring (the F2 generation) will not be considered “exposed” and a phenotype in the F2 generation would represent transgenerational inheritance. Epigenetic transgenerational inheritance may provide a means by which parental drug use can influence several generations of offspring. Interestingly, in *C. elegans*, environment-induced epigenetic marker changes have been shown to be inherited by at least 14 generations, suggesting that

transgenerational inheritance may persist past the F2 generation (Klosin *et al.*, 2017). There is a particular interest in the persistence of transgenerational effects of drug exposure on drug-related phenotypes, but this review will cover a wide range of behavioral and neurobiological effects of paternal exposure.

Alcohol

Alcohol is the most widely abused drug in the USA (Center for Behavioral Health Statistics and Quality, 2015). Its actions on the brain are mediated through several neurotransmitter systems, including glutamatergic and GABAergic signaling (Koob, 2014). Despite alcohol's widespread use, only approximately 30% of adults in the United States will develop an alcohol use disorder (Grant *et al.*, 2015), including symptoms such as dependence and/or withdrawal. Genetic factors are largely responsible for the differential vulnerability, with heritability of alcohol abuse/dependence estimated to be 50–70% (Ho *et al.*, 2010). However, the genetic factors alone cannot completely explain the pattern of inheritance of alcohol abuse disorders (Schuckit *et al.*, 1972; Cloninger *et al.*, 1981).

Although the effects of *in utero* ethanol exposure are largely defined, the effects of paternal exposure to alcohol on offspring development and behavior are less clear (Table 1). Alcohol-sired Sprague Dawley rats demonstrated learning and memory deficits, including impairments in spatial learning (Wozniak *et al.*, 1991). Additionally, alcohol-sired Swiss Webster mice displayed increased latencies to reach a choice point in a T-maze (Abel & Lee, 1988). Cognitive deficits of alcohol-sired male offspring also include attention deficits and increased impulsivity, as observed in ICR mice (Kim *et al.*, 2014). Alcohol-sired male Swiss Webster mice show decreased fear and increased aggression (Meek *et al.*, 2007). Paternal ethanol exposure results in blunted acute and chronic stress-related phenotypes in male 129Sv/ImJ × C57BL/6J mice (Rompala *et al.*, 2016). Paternal exposure to alcohol has also been associated with increased anxiety and depression in female Kunming mice (Liang *et al.*, 2014).

Alcohol-sired offspring additionally show differential response to drugs of abuse. Alcohol-sired male 129Sv/ImJ × C57BL/6J mice and C57BL/6J mice had reduced ethanol preference and consumption but exhibited enhanced sensitivity to the anxiolytic and motor-enhancing effects of ethanol (Finegersh & Homanics, 2014; Rompala *et al.*, 2017). It is likely that the decreased ethanol consumption was due to increased sensitivity to alcohol. These effects were male-specific with no observed differences in alcohol-sired female offspring. Interestingly, alcohol-sired male and female Sprague Dawley offspring show increased sensitivity to amphetamine (Abel, 1993). Taken together, these studies suggest that alcohol-sired offspring are more sensitive to alcohol and amphetamine, which can be interpreted as a protective phenotype, with the increase in ethanol sensitivity actually resulting in decreased ethanol consumption and preference.

Paternal alcohol exposure also results in neurobiological alterations in offspring. F0 fathers exposed to alcohol produce F1 Sprague Dawley rats that display cortical thickening (Jamerson *et al.*, 2004), which may indicate changes in development such as altered synaptic pruning or developmental apoptosis. Paternal exposure results in hyperactivity in male

Sprague Dawley rats, and this effect is normalized by treatment with physostimigine, a reversible cholinesterase inhibitor, suggesting cholinergic deficits in alcohol-sired offspring (Abel, 1994). Alcohol also mediates neurobiological changes highly relevant to drugs of abuse. Brain-derived neurotrophic factor (BDNF) has a well-known role in synaptic plasticity, and has been implicated in response to multiple drugs of abuse (Barker *et al.*, 2015). BDNF expression has been shown to mediate alcohol drinking behaviors in rodents (Pandey, 2016), with increased BDNF in the ventral tegmental area (VTA) resulting in decreased alcohol consumption (Raivio *et al.*, 2014). Alcohol-sired male 129Sv/ImJ × C57BL/6J mice and C57BL/6J mice showed increased *Bdnf* mRNA expression in the VTA (Finegersh & Homanics, 2014; Rompala *et al.*, 2017), which may underlie the observed decrease in alcohol consumption. Additionally, Finegersh & Homanics (2014) identified decreased DNA methylation at the *Bdnf* promoter in the VTA of male 129Sv/ImJ × C57BL/6J mice. This epigenetic change may be the mechanism that results in increased VTA *Bdnf*, and ultimately decreased alcohol consumption. Additionally, alcohol-sired male ICR mice showed decreased dopamine transporter (DAT) expression in the cortex and striatum and hypermethylation of the *Dat* gene (Kim *et al.*, 2014). Furthermore, these alcohol-sired male ICR mice expressed an attention deficit hyperactivity disorder (ADHD)-like phenotype, with increased activity, increased impulsivity, and decreased attention. DAT is a regulator of dopamine reuptake, and is known to be dysregulated in the frontostriatal dopamine system in ADHD (Faraone & Biederman, 1998). Thus, paternal alcohol exposure appears to affect DAT promoter methylation in offspring, which may be responsible for the observed differences in DAT expression, and ultimately producing an ADHD-like phenotype. The observed decrease in DAT expression is contradictory with the observed increased sensitivity to amphetamine in alcohol-sired male and female Sprague Dawley offspring (Abel, 1993). Amphetamine is a DAT inhibitor (Heikkila *et al.*, 1975; Horn, 1990), and decreased expression of DAT via knockdown results in decreased locomotor stimulant response to amphetamine (Cagniard *et al.*, 2014). However, it is important to note that these studies were completed in different species, and to our knowledge, no studies have assessed if there is an effect of paternal alcohol exposure on DAT expression in Sprague Dawley offspring.

These studies provide evidence of detectable and behaviorally significant multigenerational effects of paternal alcohol exposure on learning and memory, fear, and stress-related phenotypes in offspring. However, these effects may be sex-specific, with only male offspring exhibiting changes in attention (Kim et al., 2014), aggression (Meek *et al.*, 2007), and alcohol sensitivity (Finegersh & Homanics, 2014; Rompala *et al.*, 2016, 2017). Additionally, it is unclear if any of the observed effects are transgenerational, as only F1 offspring have been assessed, which warrants assessment in additional generations.

Cocaine

Approximately 15% of Americans will use the psychostimulant cocaine within their lifetime (Center for Behavioral Health Statistics and Quality, 2015). The rewarding effects of cocaine are largely mediated by blocking the dopamine transporter to increase dopamine levels in the nucleus accumbens (Kuhar *et a*l., 1991). Differences in baseline dopamine signaling are correlated with differential susceptibility to cocaine abuse (Volkow *et al.*, 1999). Genetic

factors account for approximately 50% of the inter-individual differences in cocaine dependence (Ho *et al.*, 2010). Despite the high heritability of cocaine dependence, very few genome-wide studies have investigated cocaine dependence (Pierce *et al.*, 2018). A recent study identified a single nucleotide polymorphism in FAM53B significantly associated with cocaine dependence (Gelernter *et al.*, 2014). Thus, although genetic factors contributing to susceptibility to cocaine abuse have been identified, there is still a large missing heritability, which may be accounted for by multigenerational and transgenerational inheritance.

Current research has identified numerous multigenerational effects of paternal cocaine exposure (Table 2). Changes in baseline locomotor activity were identified in adolescent offspring (PND16) of male Long Evans rats exposed to cocaine, with both male and female offspring displaying hyperactivity (Abel *et al.*, 1989). However, these differences were not observed in adult offspring (PND60) of male C57BL/6J mice exposed to similar levels of cocaine (30 mg/kg subcutaneous cocaine for 10 weeks in Long Evans rats compared to 20 mg/kg subcutaneous cocaine for 10 weeks in C57BL6/J mice) (Killinger *et al.*, 2012). These results suggest differential effects of paternal cocaine on adolescent offspring compared to adult offspring. Additionally, it is possible that the genetic background (inbred for C57BL6/J vs. outbred for Long Evans rats) may have significantly affected response to cocaine in the sire, and thus behavioral effects on the offspring. Still, a recent study by Fischer *et al.* (2017) identified that male, but not female, offspring of cocaine-exposed male C57BL/6J mice displayed increased baseline locomotor activity; results that are contrasting with those of Killinger *et al.* (2012). It is possible that seemingly minor alterations in behavior protocol (such as extensive handling prior to open field testing in Killinger *et al.*, 2012) could be responsible for the observed differences between male offspring of cocaine-exposed C57BL/6J. Additionally, Fischer et al. (2017) analyzed male and female offspring separately, whereas Killinger *et al.* (2012) analyzed male and female offspring together. This key difference in statistical analysis may have altered the power to detect an effect of paternal exposure within each sex.

Notably, a number of studies have found conflicting phenotypes in cocaine-sired mice. Cocaine-sired adolescent Long Evans rats (PND35) displayed increased perseverance in a T-maze learning task (Abel *et al.*, 1989). Additionally, in a self-administration model of paternal exposure, cocaine-sired adult male Sprague Dawley rats displayed impaired spatial memory, as assessed by a hippocampus-dependent spatial object recognition task (Wimmer *et al.*, 2017). Cocaine-sired CD1 mice displayed attention and spatial working memory deficits, as assessed by a 5-arm maze (He *et al.*, 2006). However, cocaine-sired C57BL/6J mice did not display deficits in a different form of hippocampus-dependent learning, the Morris water maze (Killinger *et al.*, 2012; Fischer *et al.*, 2017). Cocaine-sired male Sprague Dawley rats did not display deficits in a hippocampus-independent novel object recognition task (Wimmer *et al.*, 2017). The Wimmer *et al.* (2017) study suggests that the hippocampus and hippocampus-dependent learning may be more susceptible to the effects of paternal cocaine exposure. However, multiple factors related to experimental design may also explain these inconsistencies. For example, experimenter-administered exposure was utilized in Killinger *et al.* (2012) and Abel *et al.* (1989), but self-administration models were used in Wimmer *et al.* (2017) and He *et al.* (2006). These techniques would result in differential cocaine levels, with higher peak plasma levels in He *et al.* (2006) and Wimmer *et al.* (2017).

In addition, effects of paternal cocaine exposure may be species- or strain-specific. For example, Long Evans and Sprague Dawley rats differ in their behavioral response to cocaine (Horowitz *et al.*, 1999). Despite contrasting results, together, these studies provide support for cognitive deficits in cocaine-sired offspring.

Anxiety and depressive-like phenotypes have also been assessed in subsequent generations following paternal cocaine exposure. Only cocaine-sired male Sprague Dawley offspring displayed increased anxiety-like behaviors as measured by novelty-induced hypophagia and defensive burying tasks, relative to saline-sired males and cocaine-sired female offspring (White *et al.*, 2016). In Killinger *et al.* (2012), differences in anxiety-relevant behaviors were not observed in cocaine-sired C57BL/6J mice, as measured by open field activity and elevated plus maze. However, in Fischer *et al.* (2017), decreased time in the open arms of the elevated plus maze was detected in male cocaine-sired C57BL/6J offspring, but not female offspring. It is important to note though, as mentioned above, that Fischer *et al.* (2017) analyzed male and female offspring separately, whereas Killinger *et al.* (2012) analyzed male and female offspring together, which may have altered the power to detect an effect of paternal exposure within each sex. In addition, it is possible that these contrasting results may be a reflection of species-specific effects, differential sensitivity of specific anxiety behavioral paradigms or differences in cocaine exposure paradigms. With regards to depressive-like behaviors, no differences were observed in cocaine-sired Sprague Dawley rats (White *et al.*, 2016) or C57BL/6J mice (Fischer *et al.*, 2017), as measured by the forced swim test. However, differences were observed in cocaine-sired C57BL/6J mice, as measured by the tail suspension test, with cocaine-sired offspring displaying increased immobility (Killinger *et al.*, 2012). Although both of these behavioral tests assess behavioral despair, they appear to have different underlying neural correlates (Chatterjee *et al.*, 2012). For example, only forced swim test, not tail suspension test, shows predictive validity for the negative symptoms of schizophrenia. Taken together, these studies provide evidence for alterations in mood systems in cocaine-sired offspring that warrant further study.

Cocaine-sired offspring also show differential response to psychostimulants. Cocaine-sired male and female C57BL/6J mice offspring displayed increased cocaine-and amphetamine-induced locomotor activity, representing increased sensitivity to psychostimulants (Fischer *et al.*, 2017). In addition, Cocaine-sired female C57BL/6J mice offspring displayed decreased cocaine-conditioned place preference at a lower dose of cocaine (5 mg/kg), but not at a higher dose of cocaine (10 mg/kg), suggesting a shift in the dose– response curve of cocaine reward in cocaine-sired female offspring (Fischer *et al.*, 2017). Furthermore, cocaine-sired Sprague Dawley rats acquired cocaine self-administration more slowly and had decreased levels of cocaine intake relative to controls (Vassoler *et al.*, 2013), suggesting a protective effect against cocaine use. This protective effect occurred only in males, with no differences observed in female offspring.

Attributed to the outbred nature of Sprague Dawley rats and the variability in response to cocaine, rats can be divided into high and low responders to the psychomotor stimulant properties of cocaine (Allen *et al.*, 2007; Mandt & Zahniser, 2010). In a study by Le *et al.* (2017), Sprague Dawley rats were trained to self-administer cocaine and then separated into “Addict” F0 rats (top 25% of responders) and “Non-addict” F0 rats (bottom 40% of

responders). Following separation into “Addict” F0 and “Non-addict” F0 rats, they were bred with naïve females to generate F1 and F2 offspring. The “Addict” F1 and F2 offspring displayed increased cocaine self-administration, while no effect on cocaine self-administration was detected in the “Non-addict” F1 and F2 offspring (Le *et al.*, 2017). Previous studies that have separated mouse drug-response into high and low responders have identified numerous genetic differences between these sub-populations (Radcliffe *et al.*, 2006; He *et al.*, 2008; Belknap *et al.*, 2013). These findings provided support for a gene by environment interaction that can greatly alter the effects of paternal cocaine exposure. Future studies parsing apart the effect of paternal cocaine on cocaine-seeking vs. cocaine-intake in offspring, while controlling for factors such as genetic background, may serve to clarify this interaction.

Cocaine-sired offspring exhibit neurobiological changes that may be mediating the observed behavioral effects. Relevant to the observed differences in learning and memory, cocaine-sired male Sprague Dawley rats displayed reductions in NMDA receptor-mediated hippocampal synaptic plasticity, with impaired long-term potentiation (LTP) and decreased levels of D-serine (Wimmer *et al.*, 2017). Relevant to the observed differences in anxiety and depressive-like behaviors, cocaine-sired male Sprague Dawley offspring showed increased mRNA and protein expression of corticotropin-releasing factor receptor 2 (CRF-R2) in the hippocampus (White *et al.*, 2016). Changes in CRF levels have been shown to contribute to anxiety-like behaviors associated with cocaine withdrawal (Richter & Weiss, 1999; Morisot *et al.*, 2014, 2018). Therefore, changes in CRF-R2 may mediate the alterations in anxiety-related behaviors. Additionally, altered CRF signaling in the hippocampus could result in hippocampal deficits, and in turn, deficits in hippocampal-dependent learning (Blank *et al.*, 2002).

An additional neurobiological change associated with paternal cocaine exposure is alterations in BDNF which plays a critical role in regulating structural plasticity in dopaminergic neurons important for mediating the effects of drugs of abuse (Collo *et al.*, 2014). Specifically, cocaine-sired Sprague Dawley offspring display increased medial prefrontal cortex (mPFC) BDNF mRNA and protein levels (Vassoler *et al.*, 2013). Additionally, elevation of BDNF level in cocaine-sired offspring was shown to correlate with cocaine intake of the F0 Sprague Dawley male (Le et al., 2017). Also, an increased association of acetylated histone H3 with *Bdnf* promoters was observed in the mPFC of cocaine-sired Sprague Dawley rats, which suggests a potential epigenetic mechanism that may mediate the multigenerational phenotype (Vassoler *et al.*, 2013). It was previously observed that increased BDNF in the mPFC blunts the behavioral effects of cocaine, which may explain the protective effect of paternal cocaine exposure on cocaine self-administration in offspring (Berglind *et al.*, 2007).

Together, these findings provide support for multigenerational effects of cocaine exposure on cognitive measures, anxiety phenotypes, and depression-like phenotypes. Importantly, convergent evidence supports alterations in self-administration in cocaine-sired offspring; although this effect may be mediated by yet to be identified factors. This suggests increased vulnerability to changes in mental health in cocaine-sired offspring. Critically, there are

currently few reports of transgenerational inheritance of these effects, which warrants future studies.

Opioids

There is currently an opioid overdose epidemic in the USA (Calcaterra *et al.*, 2013). Increases in the use of prescription opioids, such as oxycodone, has resulted in a significant shift to heroin abuse and subsequent overdose deaths (Dasgupta *et al.*, 2014). Both prescription opioids and heroin produce their rewarding properties via mu-opioid receptors in the ventral tegmental area and nucleus accumbens (Britt & Wise, 1983). Approximately 43–60% of variability in opioid abuse/dependence is accounted for by genetic factors (Ho *et al.*, 2010). Importantly, environmental factors such as family relationships and peer groups, can affect vulnerability to opioid abuse (Jedrzejczak, 2005). Additionally, parental opioid exposure may significantly enhance substance abuse liability in subsequent generations.

The majority of multigenerational and transgenerational opioid exposure studies have involved maternal opioid exposure (Byrnes, 2005; Byrnes *et al.*, 2011, 2013; Johnson *et al.*, 2011; Vassoler *et al.*, 2014, 2016, 2017, 2018). However, a few studies have investigated behavioral and neurobiological differences in the offspring of opioid-exposed sires (Table 3).

Morphine exposure in adult male Sprague Dawley rats resulted in increased anxiety-like behavior in male and female offspring, as assessed by elevated plus maze and open field testing (Li *et al.*, 2014). Similarly, heroin-exposure in Sprague Dawley sires resulted in F1 male offspring with increased anxiety-like behavior, as assessed by open field activity and elevated plus maze performance (Farah Naquiah *et al.*, 2016). Additionally, these offspring exhibited increased aggressive behavior as evaluated by the resident intruder test (Farah Naquiah *et al.*, 2016). The increased anxiety and aggressive behavior was also observed in heroin-sired F2 offspring, providing evidence for transgenerational inheritance, but were not passed on to the 3rd generation (F3). Interestingly, these behavioral alterations (i.e. increased anxiety and aggression) mirrored the behavioral response in the F0 heroin-exposed males, resembling opioid withdrawal behaviors (Tidey & Miczek, 1992; Grasing *et al.*, 1996), without any opioid exposure. Opioid withdrawal is associated with increased CRF (Ingallinesi *et al.*, 2012; Umathe et al., 2012; Park *et al.*, 2013), which has been linked to increased anxiety and aggressive behaviors (Bruchas *et al.*, 2009; Carpenter *et al.*, 2009). Therefore, it is possible, though untested, that opioid-sired offspring exhibited increased CRF levels, which may increase vulnerability to opioid abuse (Piazza *et al.*, 1991; Sinha, 2001, 2008, 2009); direct assessment of neural correlates to the observed behavioral alterations should be performed to definitively elucidate these links.

In addition, opioid exposure in F0 males may alter sensitivity to opioids in offspring. Although the effects of paternal opioid exposure on the locomotor stimulant or rewarding properties of opioids in subsequent generations have not yet been assessed, morphine two-bottle choice was assessed in pubertal Wistar male and female rats from opioid-exposed sires (Pooriamehr *et al.*, 2017). Though this study did not detect an effect of paternal morphine exposure on morphine two-bottle choice, it is worth noting that when both dam and sire were exposed to chronic morphine, F1 male and female offspring displayed

increased morphine consumption. Additional studies have assessed sensitivity to the antinociceptive properties of opioids in opioid-sired offspring. Importantly, there is a significant association with analgesic sensitivity and abuse liability, with enhanced angelsic sensitivity associated with increased risk of abuse (Franklin, 1989, 1998). Therefore, assessing antinociceptive properties of opioids can serve as a proxy for understanding opioid reward. A recent study showed that chronic morphine treatment in Wistar rat sires did not affect morphine-induced antinocieption in the offspring as assessed by the formalin pain test (Pachenari *et al.*, 2018). However, in a separate study, exposure to a single dose of morphine in adult male Sprague Dawley rats prior to breeding resulted in F1 male offspring that exhibited enhanced antinociceptive effects of morphine in the hot plate assay (Cicero *et al.*, 1995). Conversely, there was no effect of morphine on nociception in morphine-sired female offspring (Cicero *et al.*, 1995). Similarly, a chronic exposure to morphine in adult male Wistar rats resulted in F1 male offspring with enhanced analgesic effects of morphine in the tail-withdrawal assay that did not persist into a second generation (Vyssotski, 2014). Despite F1 female offspring not exhibiting this phenotype, F2 female offspring showed enhanced analgesic effects of morphine (Vyssotski, 2014). These findings suggest that the effects of paternal morphine exposure may display complex sex by generation interactions.

The mechanisms underlying the sex differences observed in offspring derived from opioid-exposed fathers is not yet understood. It is well-established that females and males differ in their sensitivity to opioids in most analgesic assays (Craft, 2008; Loyd *et al.*, 2008), with males consistently exhibiting enhanced sensitivity to the antinociceptive properties (Cicero *et al.*, 1996, 1997; South *et al.*, 2009). It is worth noting that maternal opioid exposure also results in sex-specific differences in opioid analgesia, with male offspring also displaying enhanced sensitivity to the antinociceptive properties of opioids (Byrnes *et al.*, 2011). There are numerous aspects of the endogenous opioid system that are divergent based on sex; potential mechanisms that may underlie these differences include distribution of mu-opioid receptors or estrogenic effects on endogenous opioid signaling (Vathy, 2002; Craft, 2008; Loyd *et al.*, 2008). Importantly, paternal opioid exposure has been shown to influence endogenous opioid signaling in a sex-dependent manner (Cicero *et al.*, 1991). Morphine-sired female offspring, but not male offspring, exhibited increased hypothalamic levels of beta-endorphin, an endogenous ligand for the mu-opioid receptor (Cicero *et al.*, 1991). Increased beta-endorphin levels can result in opioid receptor desensitization and tolerance (Petraschka *et al.*, 2007), therefore, this mechanism may explain the lack of antinociceptive properties of morphine in opioid-sired female offspring. Taken together, paternal opioid exposure may increase the risk of opioid vulnerability in offspring in a sex-dependent manner.

Converging evidence from recent studies suggests that opioid-exposed sires produce offspring with alterations in synaptic plasticity, which plays a significant role in the pathogenesis of anxiety (Kheirbek & Hen, 2011) and addiction (Luscher & Malenka, 2011). Long-term potentiation, the enhancement of synaptic strength that results from synchronous firing of connecting neurons (Bliss & Lomo, 1973), is one form of synaptic plasticity. Hippocampal LTP was decreased in offspring of morphine-exposed sires (Sarkaki *et al.*, 2008). On the basis of deficits in hippocampal LTP, it is likely that opioid-sired offspring would display deficits in hippocampal learning and memory. It is worth noting that to our

knowledge only one study (Li *et al.*, 2014) assessed potential deficits in learning and memory in opioid-sired offspring and found no difference using the Morris water maze. Importantly, the Morris water maze was assessed in Sprague Dawley rats, whereas the differences in hippocampal LTP were assessed in Wistar rats. In addition, it remains to be determined if other cognitive domains are altered. Further studies investigating learning and memory in opioid-sired offspring may yield additional information regarding potential learning and memory deficits.

Morphine-sired Sprague Dawley offspring also displayed reduced dendritic length and branching in the dentate gyrus of the hippocampus, another neural correlate of synaptic plasticity (Li *et al.*, 2014). Moreover, offspring exhibited decreased levels of insulin-like growth factor 2 (IGF-2) in the granular zone of the dentate gyrus (Li *et al.*, 2014). Increased levels of IGF-2 have been shown to enhance neurogenesis and dendritic plasticity (Fernandez & Torres-Aleman, 2012). Together, these results support aberrant synaptic plasticity in the hippocampus of opioid-sired offspring, which might underlie the observed differences in anxiety-relevant behaviors (Li *et al.*, 2014; Farah Naquiah *et al.*, 2016). Importantly, Li *et al.* (2014), were able to reverse the increased anxiety in morphine-sired offspring by overexpressing hippocampal IGF-2 during adolescence, providing a direct link between hippocampal synaptic plasticity and the anxiety-prone opioid-sired offspring.

From these studies, it is clear that paternal opioid exposure, even a single exposure, can influence behavior and neurobiological characteristics of subsequent generations. Multiple lines of evidence suggest that opioid-sired offspring exhibit increased withdrawal-like behaviors and synaptic plasticity deficits. These alterations, combined with altered sensitivity to the antinociceptive properties of opioids combine to suggest that opioid-sired offspring may exhibit increased vulnerability to opioid abuse. As of yet, studies have not investigated the impact of paternal opioid exposure on self-administration of opioids. Future studies assessing self-administration of opioids in the paternal drug exposure paradigm are warranted to investigate the potential influence of motivated drug-seeking by self-administration.

Nicotine

It was estimated in 2016, that 15.5% of adults in the USA were current smokers, and approximately 75% of these individuals smoked daily (Center for Behavioral Health Statistics and Quality, 2015). Tobacco smoke consists of approximately 4000 ingredients, which includes nicotine, the primary addictive agent (Stolerman & Jarvis, 1995; Mishra *et al.*, 2015). Nicotine's reinforcing and rewarding properties are produced by binding to nicotinic acetylcholine receptors (nAChRs) on dopaminergic neurons in the mesolimbic dopamine system, resulting in increased dopamine release in the nucleus accumbens (Barrett *et al.*, 2004; Balfour, 2009). There is a large genetic component in smoking-related behaviors. The heritability of smoking initiation is estimated to be 44% and the heritability of nicotine dependence is estimated to be 75% (Vink *et al.*, 2005). Genome-wide association and candidate gene studies in humans have identified genetic factors that underlie smoking-related behaviors. For example, variants in the genes that encode three nAChR subunits (*CHRNA5, CHRNA3, CHRNB4*) are associated with smoking heaviness and delayed

smoking cessation (Bierut & Tyndale, 2018). Despite the success of finding human genetic variants that underlie differences in nicotine dependence, variation in these genes alone does not explain heritability of smoking-related behaviors. Environmental factors, such as peer smoking, influence smoking initiation and dependence (Hu *et al.*, 2006), and also interact with genetic factors to produce selective genotype-dependent effects (Johnson *et al.*, 2010). Additionally, parental smoking status affects smoking initiation in adolescents, with children who have parents that are current smokers exhibiting increased likelihood to become smokers (Vuolo & Staff, 2013; Kandel *et al.*, 2015). However, the child's likelihood of initiating smoking is decreased if the parent is a past-smoker instead of current smoker (Kandel *et al.*, 2015), which suggests that the relationship between parental smoking and smoking initiation in children is not purely genetic. Therefore environmental factors, including paternal nicotine exposure, may account for the remaining risk for smoking initiation and nicotine dependence.

Recent studies suggest that paternal nicotine exposure may effect behavioral and neural development in offspring (Table 4). A recent study by Vallaster *et al.* (2017) exposed male C57BL6/J mice to nicotine in drinking water (200 μg/mL free base in drinking waking for 5 weeks) and then assessed behavior in offspring. This exposure paradigm results in high levels of nicotine in the bloodstream, nicotine dependence, and somatic withdrawal symptoms in the exposed animals (Zhao-Shea *et al.*, 2013). In the F1 offspring, no differences were observed in baseline activity, as assessed by open field behavior, although other phenotypic changes were seen (Vallaster *et al.*, 2017). In contrast, a study by Dai *et al.* (2017) utilized two alternate nicotine exposure paradigms and identified differences in baseline activity in the open field. In the study by Dai *et al.* (2017), C57BL6/J mice were exposed to either chronic nicotine injections (F1-nic; 0.05 mg/ 100 g free-base nicotine, i.p., 4x daily for 5 weeks) or chronic tobacco smoke (F1-smo; 2x daily for 1 h for 5 weeks). One criticism of an oral nicotine paradigm, as used in Vallaster *et al.* (2017), is that it does not appropriately mimic smoking behavior, and does not result in the fluctuations of plasma nicotine levels seen in cigarette smokers (Benowitz *et al.*, 1982). It is possible that the difference in nicotine exposure paradigms resulted in the inconsistent effect of paternal nicotine on locomotor activity in the offspring.

In addition to basal locomotor activity, anxiety and depressive-like phenotypes have been assessed in F1 offspring of F0 fathers exposed to nicotine. No differences were observed between nicotine-sired and control-sired offspring in anxiety-like behavior, as assessed by elevated plus maze (Dai et al., 2017; Vallaster *et al.*, 2017). However, offspring from both chronic nicotine injections (F1-nic) and chronic tobacco smoke (F1-smo) displayed reduced depressive-like behaviors, as assessed by the forced swim test (Dai *et al.*, 2017). Decreased depressive-like behavior suggests alterations in neurotransmitter systems, possibly including dopaminergic and serotoninergic systems (Zangen *et al.*, 2001). Paternal nicotine exposure (F1-nic) induced activation of the Wnt4 pathway in nicotine-sired C57BL/6J offspring, as identified by mRNA sequencing and then confirmed by protein analysis. Specifically, the levels of two key proteins in Wnt4 signaling, WNT4 and Dishevelled 2 (DVL2) were increased in F1 brain tissue (Dai *et al.*, 2017). Disruption of Wnt signaling is seen in bipolar disorder and major depressive disorder (Voleti & Duman, 2012), and knockdown of Wnt signaling genes results in depressive-like phenotypes (Zhou et al., 2016). Alternatively, anti-

depressants activate Wnt signaling (Okamoto *et al.*, 2010). Thus, activation of the Wnt signaling pathway may underlie the observed decrease in differences in depressive-like behavior seen in the nicotine-sired offspring.

Paternal nicotine exposure may affect nicotine response in offspring. Although there was no effect on nicotine-induced suppression of locomotor activity or nicotine self-administration, offspring displayed a protective response to toxic levels of nicotine (Vallaster *et al.*, 2017). At the highest levels of nicotine in the self-administration test, nicotine-sired male and female offspring survived for days longer than the control-sired offspring, suggesting a protective effect of paternal exposure to high levels of nicotine. Upon further investigation, this protective effect was dependent on chronic treatment with nicotine. When offspring were exposed to a single toxic nicotine exposure (5.5–8.5 mg/kg for males, 2–8 mg/kg for females), there was no observed difference in survival rates between nicotine-sired and control-sired mice. However, if mice received 6 days of chronic nicotine, and then a lethal nicotine challenge exposure, male nicotine-sired offspring exhibited a tolerance to the lethal dose compared to female nicotine-sired offspring and both male and female control-sired offspring. These sex differences in tolerance to high doses of nicotine were not observed when the chronic nicotine was delivered via the self-administration paradigm prior to the high dose nicotine challenge. One of the key differences between these two paradigms is in length of prior exposure to nicotine (15+ days in the self-administration paradigm vs. 6 days in the chronic preexposure paradigm). This suggests that there may be a sex difference in response chronic nicotine in nicotine-sired offspring, with male offspring acclimating after only 6 nicotine exposure, but female offspring requiring more exposures.

Current studies assessing the behavioral and neural effects of paternal nicotine exposure are limited. However, recent studies suggest that paternal exposure can alter depressive-like and anxiety-relevant behaviors and impose a protective effect to high levels of nicotine. Future studies assessing additional behavioral effects and identifying the neural correlate of decreased depressive-like behaviors in nicotine-sired offspring are warranted.

Concluding remarks

Paternal drug exposure is associated with numerous significant alteration to the behavior and neurobiology of offspring and subsequent generations. The reviewed studies have focused on cognitive deficits, anxiety and depression-like phenotypes, drug response, and neurobiological correlates. In contrast with the human literature suggesting that paternal drug exposure results in increased vulnerability to drug abuse in offspring, results from preclinical studies suggest a protective effect of paternal drug exposure. Alcohol-sired offspring displayed reduced alcohol drinking (Finegersh & Homanics, 2014), nicotine-sired offspring displayed a protective effect to toxic levels of nicotine (Vallaster *et al.*, 2017), and cocaine-sired offspring displayed reduced cocaine conditioned place preference (Fischer *et al.*, 2017) and self-administration (Vassoler *et al.*, 2013). Notably, however, preliminary findings in the area of paternal opioid exposure suggest increased vulnerability to opioid abuse in offspring. To our knowledge, there are no studies assessing opioid reward or self-administration in opioid-sired offspring, which will be necessary to determine this effect. Additionally, it is important to note that paternal exposure to multiple drug classes (opioids,

cocaine, alcohol) also resulted in increased anxiety-relevant behaviors, which may increase vulnerability to drug abuse (Piazza *et al.*, 1991; Sinha, 2001, 2008, 2009). The increases in anxiety and aggression, in combination with deficits in learning and memory suggest maladaptive neuroadaptations in multiple neural systems.

Converging evidence from multiple studies and drug classes supports a role of altered CRF and BDNF in mediating changes in drug-sired offspring. Additionally, paternal exposure to both cocaine and opioids resulted in deficits in hippocampal plasticity. Together, these studies have identified multiple changes in neural function in drug-sired offspring.

The transgenerational effects of paternal drug exposure may not be straightforward, with marked differences observed in rats compared to mice, and in male offspring compared to female offspring. Additional considerations include the administration and methodology used for the F0 exposure. Studies in this review ranged from single exposure models to chronic self-administration models. Interpretation of these results and subsequent extrapolation to human drug use should take these different models into account. Additionally, one largely unanswered phenomenon is the sex-differences in behavioral responses in drug-sired offspring. Paternal exposures to multiple drug classes (cocaine, alcohol, opioids) result in largely male-specific deficits.

Studies exploring the potential mechanisms underlying these multigenerational and transgenerational effects of paternal drug exposure are still extremely limited. Epigenetic mechanisms may be mediating the transgenerational inheritance of these alterations in behavior and neurobiology (Vassoler & Sadri-Vakili, 2014; Yuan *et al.*, 2016). Notably, very few studies have looked beyond the first generation, therefore providing evidence only for multigenerational inheritance rather than transgenerational. For the effect to be truly non-genomic epigenetic inheritance, it must persist past the first generation. Regardless, the significance of an impact on the first generation warrants future studies delineating the effects of paternal exposure on the behavior and neurobiology of subsequent generations.

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Abbreviations

BDNF	brain-derived neurotrophic factor
CRF	corticotrophin-releasing factor
CRF-R2	corticotrophin-releasing factor receptor-2
IGF-2	insulin-like growth factor 2
mPFC	medial prefrontal cortex
LTP	long-term potentiation
nAChRs	nicotinic acetycholine receptors

PND	post-natal day
VTA	ventral tegmental area

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Table 1.

Multigenerational and transgenerational effects of paternal exposure to alcohol on behavioral and neural function.

F0 exposure	F0 exposure age	Species	Generation tested	Sex tested	Phenotype (in offspring)	Effect	Source
Chronic: 20% ethanol for 56 days	9–17 weeks	Swiss Webster Mice	F1	Males & Females	T-maze at PND16	Increased latency	Abel & Lee (1988)
					Locomotor activity at PND30	Decreased locomotor activity	
					Amphetamine-induced locomotor activity at PND100	No effect	
Chronic: intubated twice daily with 3 g/kg ethanol for 4 months	10–20 weeks	Sprague Dawley Rats	F1	Males	Passive avoidance	Decreased trials to meet criterion	Abel (1994)
					Physostigmine-induced locomotor activity	Decreased locomotor activity	
Chronic: intubated twice daily with 3 g/kg ethanol for 4 months	10–20 weeks	Sprague Dawley Rats	F1	Males & Females	Amphetamine-induced locomotor activity at PND90	Increased locomotor activity	Abel (1993)
Chronic: 20% ethanol in water as sole liquid for 48 days	Adult (age not specified)	Sprague Dawley Rats	F1	Males & Females	Brain morphometry at PND28	Increased cortical thickness	Jamerson *et al.* (2004)
Chronic: 4 g/kg/day ethanol for 7 weeks	5–12 weeks	ICR Mice	F1	Males	Open field	Increased locomotor activity	Kim *et al.* (2014)
					Y-maze	Decreased spontaneous alternation behavior	
					Electrofoot shock aversive water drinking test	Increased number of attempts	
					Western blotting	Decreased DAT in the striatum	
					Methylation-specific PCR for DAT gene promoter	Increased methylation of DAT promoter	
Chronic: intubated every other day 3.3 g/kg for 4 weeks	5–10 weeks	Kunming Mice	F1	Males & Females	Elevated Plus Maze	M: No effect, F: Decreased open arm time	Liang *et al.* (2014)
					Tail Suspension Test	M: No effect, F: Increased time immobile	
					Morris Water Maze	M: Increased time to find platform, F: No effect	
Acute: 5 g/kg i.p. 20% ethanol	12 weeks	Swiss Webster Mice	F1	Males & Females	Resident-intruder test	Increased aggressive behavior	Meek *et al.* (2007)
					Defensive burying	Increased defensive behavior	

F0 exposure	F0 exposure age	Species	Generation tested	Sex tested	Phenotype (in offspring)	Effect	Source
Chronic: 35% ethanol-derived calories for 39 days	3–10 weeks	Sprague Dawley Rats	F1	Males	Radial arm maze	Impaired	Wozniak *et al.* (1991)
					T-maze	Impaired	
					Object recognition test	No effect	
Chronic: Ethanol Vapor chamber, 8 h, 5 days/week, 5 weeks	8–13 weeks	129Sv/ImJ × C57BL/6J Mice	F1	Males & Females	Ethanol two-bottle choice	M: Reduced ethanol preference, F: no effect	Finegersh & Homanics (2014)
						M: Reduced ethanol consumption, F: no effect	
					Ethanol-induced anxiolysis	M: Enhanced sensitivity to anxiolytic effects of ethanol, F: no effect	
					Ethanol-induced locomotor activity	No effect	
					Accelerating rotarod	M: Enhanced, F: no effect	
					qPCR (*Bdnf* in the VTA)	M: Increased, F: no effect	
Chronic: Ethanol Vapor chamber, 8 h, 5 days/week, 5 weeks	8–13 weeks	129Sv/ImJ × C57BL/6J Mice	F1	Males & Females Males	Stress-evoked ethanol drinking	No effect	Rompala *et al.* (2016)
					Stress-evoked polydipsia	Resistant	
Chronic: Ethanol Vapor chamber, 8 h, 5 days/week, 5 weeks	8–13 weeks	C57BL/6J Mice	F1	Males & Females	Ethanol two-bottle choice	M: Reduced ethanol preference, F: no effect	Rompala *et al.* (2017)
					Ethanol-induced anxiolysis	M: Enhanced sensitivity to anxiolytic effects of ethanol, F: no effect	
					Ethanol-induced locomotor activity	No effect	
					Accelerating rotarod	No effect	
					qPCR (*Bdnf* in the VTA)	M:Increased, F: no effect	

Table 2.

Multigenerational and transgenerational effects of paternal exposure to cocaine on behavioral and neural function.

F0 exposure	F0 exposure age	Species	Generation tested	Sex tested	Phenotype (in offspring)	Effect	Source
Chronic: 15 or 30 mg/kg, s.c. for at least 72 days	16–17 weeks	Long Evans Rat	F1	Males & Females	Open Field	Hyperactive	Abel *et al.* (1989)
					Passive Avoidance	No effect	
					T-maze	Increased trials to criterion	
Chronic: Self-administration via inhalation	4–7 weeks	CD1 Mice	F1	Males & Females	5-arm maze	Increased trials to criterion	He *et al.* (2006)
Chronic: 20 mg/kg, i.p., 10 weeks	12–24 weeks	C57BL/6J Mice	F1	Males & Females	Elevated Plus Maze	No effect	Killinger *et al.* (2012)
					Open Field	No effect	
					Tail Suspension	Increased immobility	
					Novel Object Recognition	No effect	
					Morris Water Maze	No effect	
Chronic: Self-administration (60 days)	9–18 weeks	Sprague Dawley Rats	F1	Males & Females	Cocaine self-administration	M: Reduced cocaine self-administration, F: no effect	Vassoler *et al.* (2013)
Chronic: Self-administration (60 days)	9–18 weeks	Sprague Dawley Rats	F1	Males & Females	Novelty-induced hypophagia	M: Increased, F: no effect	White *et al.* (2016)
					Defensive Burying	M: Increased, F: no effect	
					Forced Swim Test	No effect	
				Males	qPCR &Westem Blot (CRF-R2)	Increased in hippocampus	
Chronic: Self-administration (60 days)	9–18 weeks	Sprague Dawley Rats	F1	Males & Females	Object Location memory task	M: Impaired, F: no effect	Wimmer *et al.* (2017)
					Novel Object Recognition	No effect	
					LTP	M: Impaired, F: no effect	
Chronic: 20 mg/kg i.p., 75 days	8–18 weeks	C57BL/6J Mice	F1	Males & Females	Open Field	M: hyperactive F: no effect	Fischer *et al.* (2017)
					Cocaine-CPP (5 mg/kg, 10 mg/kg)	M: no effect, F: lower CPP at 5 mg/ kg, no effect at 10 mg/kg	
					Cocaine-induced locomotor activity (10 mg/kg)	M,F: Increased	
					Amphetamine-induced locomotor activity	M,F: Increased	

F0 exposure	F0 exposure age	Species	Generation tested	Sex tested	Phenotype (in offspring)	Effect	Source
					Sucrose consumption test	M: no effect, F: Increased	
					Forced Swim Test	M,F: no effect	
					Elevated Plus Maze	M: Decreased time in the open arms, F: no effect	
					Three-Chambered social interaction Test	M,F: no effect	
					Morris Water Maze	M,F: no effect	
					Water-based Y-maze	M,F: no effect	
Chronic: Self-administration (Separated into Addict F0 and Non-Addict F0)	10–14 weeks	Sprague Dawley Rats	F1, F2	Males	Cocaine Self-administration	Addict F1, F2: Increased cocaine intake, Non-addict F1, F2: Decreased cocaine intake	Le *et al.* (2017)

Table 3.

Multigenerational and transgenerational effects of paternal exposure to opioids on behavioral and neural function.

F0 exposure	F0 exposure age	Species	Generation tested	Sex tested	Phenotype (in offspring)	Effect	Source
Chronic: Sustained-released morphine pellets (3–4 weeks)	4–8 weeks	Sprague Dawley Rats	F1	Males & Females	Hypothalamic beta-endorphin levels	Male: No effect, Female: Increased	Cicero *et al.* (1991)
Acute: morphine (35 mg/ kg., i.p.)	9 weeks	Sprague Dawley Rats	F1	Males & Females	Antinociceptive activity of morphine: hot plate	Male: Enhanced sensitivity, Female: No effect	Cicero *et al.* (1995)
Chronic: morphine (32 mg/kg, 2x daily, i.p., 5 days)	16–20 weeks	Wistar Rats	F1	Males & Females	Hippocampal LTP	Reduced LTP	Sarkaki *et al.* (2008)
Chronic: morphine (increasing dosing regimen, 38 days, i.p.)	6–12 weeks	Wistar Rats	F1, F2	Males & Females	Antinociceptive activity of morphine: Tail-withdrawal latency	F1 male: Enhanced sensitivity, F1 female: No effect; F2 male: No effect, F2 female: Enhanced sensitivity	Vyssotski (2014)
Chronic: morphine (increasing dosing regimen, 10 days, i.p.)	8–10 weeks	Sprague Dawley Rats	F1	Males & Females	Elevated Plus Maze	Increased anxiety-like behaviors	Li *et al.* (2014)
					Open field	Increased anxiety-like behaviors; no effect on overall locomotor activity	
					Morris Water Maze	No effect	
					Hippocampal Dendritic Morphology	Decreased dendritic, length, dendritic branching, and dendritic spine number	
					Western Blotting (IGF-2)	Decreased levels	
Chronic: heroin (increasing dosing regimen i.p.)	6–8 weeks	Sprague Dawley Rats	F1, F2, F3	Males	Open field	FI, F2: Increased anxiety-like behaviors; F3: no effect	Farah Naquiah *et al.* (2016)
					Elevated Plus Maze	FI, F2: Increased anxiety-like behaviors; no effect on overall locomotor activity; F3: no effect	
					Resident-Intruder	FI, F2: Increased aggressive behavior; F3: no effect	
Chronic: morphine (10 mg/kg, 2x daily, s.c.. 14 days)	Adult (age not specified)	Wistar Rats	F1	Males & Females	Elevated Plus Maze	No effect	Pooriamehr *et al.* (2017)
					Sucrose Preference Test	No effect	
					Morphine Two-bottle Choice	No effect	
Chronic: morphine (increasing dosing regimen, 10 days, i.p.)	4–6 weeks	Wistar Rats	FI	Males	Formalin-induced Pain Test	Decreased duration of interphase period (quiescent phase with little to no pain behaviors)	Pachenari *et al.* (2018)

F0 exposure	F0 exposure age	Species	Generation tested	Sex tested	Phenotype (in offspring)	Effect	Source
					Morphine-induced Antinociception (2.5 mg/kg)	No effect	

Table 4.

Multigenerational and transgenerational effects of paternal exposure to nicotine on behavioral and neural function.

F0 exposure	F0 exposure age	Species	Generation tested	Sex tested	Phenotype (in offspring)	Effect	Source
Chronic: Nicotine drinking paradigm (200 μg/mL free base in water) for 5 weeks	3 −8 weeks	C57BL/6J Mice	F1	Males & Females	Open field test	No effect	Vallaster *et al.* (2017)
					Elevated Plus Maze	No effect	
					Nicotine-induced hypolocomotor assay	No effect	
					Nicotine self-administration	No effect on daily levels of nicotine administered	
						Effect on survival curve of mice at high levels of nicotine during self-administration, NIC-sired mice survived longer	
					Susceptibility to toxic nicotine injection	No effect	
					Susceptibility to toxic nicotine injection after chronic nicotine exposure	Male : more tolerant, Female: no effect	
Chronic: F1-SMO (2x daily 1 h tobacco smoke exposure for 5 weeks)	6–11 weeks	C57BL/6J Mice	F1	Males & Females	Open field test	Increased locomotor activity	Dai *et al.* (2017)
					Elevated Plus Maze	No effect	
					Novel Object Recognition	No effect	
					Social Chamber Test	Increased time in social chamber	
					Forced Swim Test	Decreased time spent immobile	
					Sucrose Preference	No effect	
Chronic: F1-NIC (0.05 mg/100 g free-base nicotine, i.p., 4x daily for 5 weeks)	6–11 weeks	C57BL/6J Mice	F1, F2	Males & Females	Open field test	F1: Increased locomotor activity, F2: no effect	
					Elevated Plus Maze	F1, F2: No effect	
					Novel Object Recognition	F1, F2: No effect	
					Social Chamber Test	F1, F2: No effect	
					Forced Swim Test	F1: Decreased time spent immobile, F2: no effect	

F0 exposure	F0 exposure age	Species	Generation tested	Sex tested	Phenotype (in offspring)	Effect	Source
					Sucrose Preference	F1, F2: No effect	