Corticostriatal deficits underlying cognitive impairments induced by fetal exposure to alcohol

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Abstract

The term Fetal Alcohol Spectrum Disorder (FASD) includes a group of diseases caused by fetal exposure to alcohol (FAE). FASD patients display heterogenous socio-emotional and cognitive deficits, particularly in the domain of executive function, which share symptoms with other neuropsychiatric disorders. Despite the availability of several preclinical models, the developmental brain defects causally linked to behavioral deficits induced by FAE remain poorly understood. Here, we first review the FAE-induced synaptic and circuit impairments in mesocorticolimbic areas involved in social and motor behaviors. Then, we consider the effects of FAE on cortical excitation/inhibition balance and its impact on both corticostriatal pathway function and cognitive abilities. In particular, we propose three non-mutually exclusive circuit models of corticostriatal dysfunctions to account for some of the FAE-induced cognitive deficits. One model posits that associative-sensorimotor imbalance causes hyper goal-directed behavior and a second model implies that alteration of prefrontal-striatal behavioral suppression circuits results in the loss of behavioral inhibition. A third model suggests that local striatal circuit deficits affect striatal neuronal ensemble function to impair action selection and performance. Finally, we discuss how pre-clinical approaches suggest potential rescue strategies for neuronal circuit defects in FASD patients.

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List of abbreviations

FASD	Fetal Alcohol Spectrum Disorder
FAS	Fetal Alcohol Syndrome
FAE	Fetal Alcohol Exposure
CDC	Centers for Disease Control and Prevention
ADHD	Attention Deficit Hyperactivity Disorder
OCD	Obsessive Compulsive Disorder
BAC	Blood Alcohol Concentration
CIE	Chronic Intermittent Ethanol
HFS	High Frequency Stimulation
LTP	Long-Term Potentiation
EPSP	Excitatory Post-Synaptic Potential
NMDAR	N-Methyl D-aspartic Acid Receptor
DG	Dentate Gyrus
VTA	Ventral Tegmental Area
AMPA	α -Amino-3-hydroxy-5-Methyl-4-isoxazolePropionic Acid Receptor
eCB	endoCannaBinoid
LTD	Long-term Depression
MSN	Medium Spiny Neuron
D1R	Dopamine Receptor 1
D2R	Dopamine Receptor 2
OFC	Orbitofrontal Cortex
PFC	Prefrontal Cortex (1,2)
DLS	DorsoLateral Striatum
DMS	DorsoMedial Striatum

M1 primary Motor Cortex

“The root of the problem is not neglect or abuse, although for many, disruptive families have compounded their problems. They [people with FASD] live in self-perpetuating ignorance, poverty, and crime because they came into the world with permanent neurological damage that could have been prevented.”

- From *Damaged Angels*, Bonnie Buxton (2004)

Introduction

The teratogenic effects of ethanol (EtOH) manifest as highly prevalent and heterogeneous somatic abnormalities as well as lifelong neurobehavioral deficits (1–3), collectively known as “fetal alcohol spectrum disorder” (FASD) (*Diagnostic and Statistical Manual of Mental Disorders 5*; American Psychiatry Association, pp. 86, 798–801, Washington DC). FASD includes fetal alcohol syndrome (FAS), partial FAS, alcohol-related birth defects, alcohol-related neurodevelopmental disorder and neurobehavioral disorder associated with prenatal alcohol exposure. Altogether these disorders affect 1 in 20 children (2). In the US, the estimated economic burden of \$4 billion/year (4) is largely due to the underdiagnosis of the disease (5), the absence of a definitive treatment (6), adverse postnatal environments (7) and the protraction of the neurobehavioral symptoms into adult patients (8–16), which often necessitate assisted living. In fact, according to the Centers for Disease Control and Prevention (CDC, <https://www.cdc.gov/ncbddd/fasd/index.html>), FASD adults have, among others, troubles with the law, inappropriate sexual conduct, drug abuse and difficulties in maintaining a job.

Over the years, several rodent models of FASD have been developed to better understand the brain deficits underlying FAE-induced behavioral impairments. Here, we discuss pre-clinical studies that focus on the neural circuit and synaptic dysfunctions involved in socio-emotional, motor and cognitive deficits induced by FAE. In particular, because of their vulnerability to the teratogenic effects of alcohol, we examine the effects of FAE on synaptic and neuronal function within corticostriatal circuits. First, we explore the idea that altered excitatory/inhibitory balance within cortical networks affects corticostriatal pathway functions. Then, we propose three different models of circuit impairments to account for the FAE-induced executive function deficits. The first model involves imbalanced function of associative-sensorimotor pathways that would favor goal-directed behavior, impair habit formation and preclude the formation or the updating of novel action-outcome associations. The second model posits that deficits in prefrontal-striatal circuits deputized to the suppression of behavioral programs promote action repetition and impair reversal learning. A third model proposes that impaired action performance originates from dysfunctions in striatal output pathways. Importantly, these models are not mutually exclusive and might emerge from complex interactions between cortical input, dopaminergic signaling and local GABAergic FAE-induced deficits. Finally, we discuss pre-clinical studies testing potential therapeutic approaches to

ameliorate aberrant behavioral traits and neurophysiological deficits induced by exposure to ethanol during development.

The socio-emotional and cognitive deficits caused by fetal exposure to alcohol

The first cases of FAS were clinically described almost 50 years ago (17). Besides the consequences on somatic and anatomical development (18), fetal alcohol exposure (FAE) particularly impairs socio-emotional processes. Socio-emotional dysfunctions span the range from hyper-irritability to heightened aggression (19,20), impaired recognition of social cues and impoverished interpersonal skills (14,21) during infancy and adolescence. Further, adults often display inappropriate maternal and sexual behavior (14,22) and unlawful conduct.

In addition to social deficits, FAE impairs “executive functions”, which are a set of cognitive abilities available to an individual to reach a desired goal (23). They include the ability to focus attention, select actions, inhibit competing behavioral patterns, and the ability to learn and retain cue/action-outcome associations to generate goal-directed behavioral responses. Once learned, those responses become automatized, or habitual. This allows for the formation of novel action-outcome associations and behavioral adaptations in the face of changing circumstances (24), a process described as cognitive flexibility. EtOH exposure during pregnancy has dramatic consequences on all these aspects of executive function. In fact, FASD symptoms include reduced attention in complex tasks and spatial working memory (25), poor action

Figure 1. FASD co-morbidities.

FASD shares clinical symptoms with other neuropsychiatric disorders, including substance abuse, attention deficits, hyperactivity, anxiety, depression and social deficits.

planning (26,27), which might be precipitated by low intelligence (28), variable degrees of hyperactivity (9) and poor response inhibition (27,29). Cognitive flexibility is also profoundly impaired in both FASD children (26,27,30,31) and adults (10). Moreover, EtOH exposure affects specific aspects of learning: FASD patients display difficulties in memorization rather than information retrieval (16,32,33) and deficits in declarative, rather than procedural, memory (34). Although several rodent models of fetal alcohol exposure (FAE) have been developed over the years (35), direct links between neuronal circuits, cognitive and socio-emotional impairments remain largely unexplored (36).

This might be particularly relevant, as a thorough understanding of the defects in brain pathways that control executive function and socio-emotional defects might support effective therapeutic interventions for FASD patients.

The cognitive and socio-emotional deficits observed in FASD patients often resemble symptoms of other neuropsychiatric disorders (37,38) (**Figure 1**) and can confound the FASD diagnosis (39). In particular, preclinical and clinical studies reported that impulsivity and hyperactivity traits appear in both FASD and attention deficit hyperactivity disorder (ADHD) (40). Obsessive-compulsive disorder (OCD) (37) and inappropriate social behavior (41), reminiscent of autism, are other secondary outcomes associated with fetal exposure to alcohol. Additionally, anxiety, depression, suicidal thoughts and drug use disorders often co-occur in patients with FASD (42). All these shared psychiatric symptoms indicate that similar neural circuit defects underlie comorbid neuropsychiatric disorders and that the investigation of brain maladaptations in one disease would be helpful to better understand a disorder with a shared symptomatology. This idea also motivates the identification of novel therapeutic interventions that, instead of curing one disorder, would treat a set of behavioral symptoms occurring in multiple diseases (Research Domain Criteria framework, NIMH). In this framework, the use of animal models of FASD might help to clarify the neuronal circuit deficits induced by fetal exposure to ethanol but also other neurodevelopmental disorders. The same approach can be applied to the identification of circuit-based rescue strategies for cognitive and socio-emotional deficits of FASD animal models. Considering that developmental exposure to alcohol impairs multiple aspects of behavior, it has been suggested that FAE might cause specific circuit and synaptic dysfunctions in brain regions deputed to the control of those behavioral traits (43). In particular, while hippocampal, mesolimbic, motor cortex and cerebellum deficits might underlie spatial learning, socio-emotional and motor behavior impairments, executive function deficits might result from synaptic and circuit dysfunctions in corticostriatal networks.

Rodent models of FASD

Animal models of fetal alcohol exposure (FAE) with face, construct and predictive validity must consider the timing and the amount of alcohol exposure, which greatly impacts blood alcohol concentration (BAC). In humans, some women unaware of their pregnancy status tend to consume large quantities of alcohol in a limited amount of time (binge drinking) and, in about 90% of the cases, drinking stops after pregnancy has been ascertained (44). However, psychological, psychiatric and environmental risk factors might promote binge-like drinking throughout pregnancy, the pattern of alcohol consumption most associated with a FASD diagnosis (45).

EtOH exerts its teratogenic effects on neural functions by interfering with the various stages of brain development (46). When alcohol is introduced into the body, BAC rises and EtOH enters fetal circulation *via* the placenta (47). EtOH metabolites, including fatty acid ethyl esters, are expelled in the meconium (48) and their levels reflect the pattern of alcohol ingestion during pregnancy (49). This is particularly relevant because EtOH exposure modalities seem to determine FASD severity: while early and

repeated exposures are the most detrimental, even one single alcohol exposure causes neurological damage (50–53). As the fetus goes through various stages of development, the timing of exposure to alcohol also determines FASD symptomatology (45). In particular, EtOH has been shown to alter various stages of brain formation and maturation (50): from neurogenesis (51), neuronal proliferation and migration (52,53), to synaptic formation and remodeling. Moreover, the amount of consumed EtOH affects BAC and impacts anatomical and behavioral function. For example, binge-drinking of alcohol could result in BAC equal or higher than 200 mg/dL (54). In this case, the probability of FASD diagnosis for the new-born is at its highest (45,54,55), even though moderate alcohol ingestion has negative consequences on cognitive function as well (56). Other than dose, timing and modality of EtOH exposure, preclinical models of FAE need to consider the various possible routes of alcohol administration, which greatly influence BAC, and the postnatal maturation of brain circuits (57–59). In particular, rodent pregnancy is considerably shorter than human gestation and, while in the latter the period of brain development is almost complete at birth, this process continues outside of the uterus for about 7-10 days in rodents (57). Thus, it is not rare to find pre-clinical studies that extend or start FAE during postnatal periods.

In laboratory settings, ingestion of alcohol can be achieved by inducing voluntary drinking of a sweetened ethanol-containing solution before and during gestation (60) or by feeding pregnant females with an ethanol-enriched liquid diet (61). Voluntary drinking allows for moderate and protracted alcohol ingestion (with BAC at 50-150 mg/dL) (60), but it poses some difficulties in controlling EtOH levels over time, partly because of the aversive properties of EtOH in rodents (62). The most reliable ways to control BAC are single or repeated intraperitoneal (i.p.) injections of EtOH, which allow for a binge-like surge (BAC: > 200 mg/dL) of circulating alcohol (63). However, injections are not the typical route of exposure and might lead to non-physiological increases of ethanol into fetal circulation (35). A binge-like consumption of alcohol in rodents can also be obtained by intragastric intubation (64–66), which induces significant surges of BAC (300-400 mg/dL) but negatively affects the well-being of the pregnant females. Lastly, chronic intermittent ethanol (CIE) exposure, which consists in cyclic periods of exposure to and withdrawal from EtOH vapor (67), induces and mimics alcohol abuse in adult rodents (68). Maintaining EtOH levels at 15-20 mg/L of air in the vapor chamber leads to stable and relatively high BAC (above 175 mg/dL), with a peak higher than 200 mg/dL (69). A great advantage of this method is that EtOH exposure can be protracted after birth as pups can be transferred with the dam in the vapor chamber, with minimal amount of stress and handling. On the other hand, inhalation is not the usual route of alcohol consumption and might irritate the respiratory tract (35), which could in turn act as a stressor. Thus, although each of those EtOH exposure protocols needs careful consideration, they provide useful pre-clinical models to study the behavioral deficits and the underlying brain dysfunctions induced by fetal alcohol exposure.

Synaptic and circuit defects underlying FAE-induced learning, socio-emotional and motor impairments

Children and adults affected by FASD exhibit brain abnormalities, including microcephaly and reduction in grey/white matter volume (70,71). Functional imaging studies further revealed that FASD patients display deficits in brain regions, including hippocampus, amygdala, basal ganglia and cerebellum, which in some cases correlate with symptom severity (72). Similarly, pre-clinical research has focused on investigating the cellular and synaptic deficits in brain areas that might underlie FAE symptoms. For example, given the involvement of hippocampal circuits in spatial navigation, FAE-induced spatial learning impairments might derive from hippocampal dysfunctions. In fact, it has been shown that prenatal alcohol exposure, *via* EtOH liquid diet or oral gavage, attenuated high-frequency stimulation (HFS)-induced long-term potentiation (LTP) of population responses in the CA1 region of both adult and adolescent rats (73,74). However, EtOH exposure limited to the first post-natal days spared excitatory postsynaptic potential (EPSP) LTP in CA1 neurons (75). Moreover, when ethanol exposure starts nine-days after the beginning of pregnancy, LTP in CA1 region is preserved at low-, or barely affected by high-, concentration of ethanol (76). These findings indicate that the early stage of brain development might be a critical period of heightened vulnerability to the deleterious effects of alcohol on hippocampal synaptic plasticity. This hypothesis has been recently challenged by the evidence that a single early adolescence ethanol exposure alters NMDAR (N-methyl d-aspartic acid receptor)-dependent LTP while leaving NMDAR-independent LTP intact (77). Thus, EtOH retains some teratogenic effects on excitatory CA1 synapse function, and perhaps other synapses, even at later stages of synaptic maturation.

While the deleterious effects of FAE on synaptic plasticity of perforant pathway to dentate gyrus (DG) inputs are sensitive to the timing of exposure as in CA1 hippocampal neurons, they appear to be sexually dimorphic. In adult male rats, although short exposure to EtOH does not affect synaptic potentiation *in vivo* (78), prolonged FAE deteriorates perforant pathway plasticity (79,80). Deficits in tetanic stimulation-induced release of D-aspartate in DG slice preparations after FAE confirm these findings (79,81). On the contrary, in adult females LTP is intact (80) and even enhanced in early adults exposed to EtOH during late developmental stages (78). The sex-specific effects on synaptic plasticity are corroborated by sexually dimorphic transcriptional FAE-induced modifications in hippocampal gene expression (82). However, the apparent sexual dimorphism of LTP deficits in the DG are challenged by slice recordings showing that FAE attenuates LTP in both sexes and LTP can be reinstated with longer stimulation protocols in adolescent rats (83). Altogether, these studies indicate that the attenuation of LTP might be the main consequence of FAE at perforant pathway synapses. However, further experiments are required to clarify the genetic, environmental, synaptic and molecular mechanisms underlying the sex-, time- and age-dependent deficits induced by FAE.

Reward-seeking and social behavior depend on meso-cortico-limbic system function (84), thus the FAE-induced impairments in these domains might derive from neuronal defects in the ventral tegmental area (VTA) and amygdala circuits. In fact, similarly to prenatal cocaine exposure and genetic dysfunctions altering glutamatergic synapse maturation (85,86), FAE strengthens excitatory inputs onto dopaminergic neurons of the ventral tegmental area (VTA) and increases the expression of GluA2-lacking AMPARs (87). These non-canonical AMPARs promote forms of anti-hebbian synaptic potentiation (85,88), which are also reported following FAE (87). Concomitantly, deregulated endocannabinoid (eCB) signaling alters pre-synaptic glutamate release properties and attenuates eCB-dependent long-term depression (LTD) (89). Thus, the loss and the gain of depression and potentiation plasticity mechanisms, respectively, may result in an over-responsivity of VTA dopamine neurons to glutamatergic inputs and set the basis for the enhanced amphetamine-seeking behavior observed in FAE rat offspring (87,89). Corroborating evidence suggests that, despite reduced hyperpolarization-induced cationic currents and up-regulated somato-dendritic D2R function, excitatory input and depolarization block deficits underlie the reduced firing frequency of VTA DA neurons *in vivo* following FAE (90). Similar to the VTA, prenatal alcohol exposure attenuates GABAergic tone and enhances LTP induced by HFS in the cortico-amygdala pathway (91), pointing to an enhanced excitatory plasticity induced by FAE in the amygdala.

Hyperactivity and altered coordination might stem from impaired cerebellar and cortico-striatal circuit function. In the cerebellum of adolescent mice, FAE reduces neuronal excitability, excitatory input strength as well as the number of Purkinje cells (92). However, prenatal ethanol exposure concomitantly promotes LTP at parallel fiber cerebellar inputs. This is thought to be a synaptic mechanism potentially underlying the increased firing activity of Purkinje cells, which is associated with motor skill learning disabilities (92). Similarly, it has been shown that EtOH exposure alters the genetic profile and the excitability of layer II/III neurons in the motor cortex, resulting in impairments in rotarod-based motor learning (93). Altogether, these studies highlight the heterogeneous effects of EtOH exposure on synaptic function, they further suggest that FAE increases excitatory synaptic function in VTA, amygdala and cerebellum to impair drug seeking behavior, sociability and motor learning in the offspring.

Executive function deficits induced by fetal alcohol exposure in rodents

The neurobehavioral studies conducted in different FAE models recapitulated most of the executive function impairments observed in FASD patients (94). A series of behavioral experiments revealed attention deficits in FAE adult rats, as evidenced by increased reaction times, augmented rates of false alarms and reduced response accuracy (95,96). Furthermore, in a delayed matching-to-place Morris Water Maze, in which animals learn to find a hidden platform, FAE male rats performed poorly at longer-, but not shorter, inter-trial intervals (97). This evidence points to impaired spatial working memory, but intact

learning at sufficiently brief inter-training intervals. The effects of FAE on learning can also be studied throughout life, starting as early as postnatal day 1 (P1) (98). The use of EtOH as a reinforcer revealed an increased acquisition together with a reduced extinction (98,99) of operant responding at infancy. Similarly, FAE increases operant responding for both EtOH and sucrose at adolescence (100,101) and lever-pressing for low-doses of psychostimulants at adulthood (87). However, FAE does not affect other learning tasks, such as the acquisition of food-reward contingencies in the Y-maze (102) or spatial learning in the Morris and T Water Mazes (103,104). Therefore, despite causing attention and working-memory deficits, FAE might increase reward sensitivity allowing, and in some cases enhancing, reward-seeking in operant tasks. These behavioral data also indicate that FAE might predispose to alcohol- and drug-seeking later in life, traits resembling the highly prevalent substance use and dependence observed in FASD patients (105).

The increased operant responding for substances of abuse and the enhanced perseverative operant responses suggest that FAE might affect goal-directed and/or habitual behavior. Recently, our laboratory tested this hypothesis by training FAE mice under random-ratio (RR) or random-interval (RI) reinforcement schedules to bias animals towards goal-directed or habitual instrumental responding, respectively (106). Although FAE mice increased lever pressing during RR training, they reduced operant responding following outcome devaluation suggesting an appropriate use of goal-directed strategies. However, these same mice retained a goal-directed pattern of responding following RI training, indicative of impaired habit formation (107). Interestingly, other studies reported that maladaptive perseverative responses underlie inflexible behavior upon changes in contextual associations. In fact, in the absence of overt learning deficits, FAE adult mice display enhanced reinstatement of previously extinguished responses (108). These impairments are associated with reversal learning deficits, indicative of altered cognitive flexibility, in both adolescent and adult FAE offspring (43,102,109–111). Again, these behavioral deficits provide a good parallel with behavioral inflexibility observed in FASD (105). The paradoxical FAE-induced deficits in both reversal learning, which suggests a more automatized behavioral responding, and habit formation, which instead points to a stronger reliance on goal-directed strategies, is intriguing. Here, we hypothesize that hyper goal-directed strategies based on previously learned action-outcome associations, and sensitive to the subjective value of a stimulus, would hinder the animal's ability to develop novel action-outcome associations, leading to inflexible behavior upon changes in external circumstances.

FASD neurobehavioral symptoms include reduced inhibition of behavioral responding, which might also underlie the heightened operant responding described above. Indeed, passive avoidance tasks, which assess the ability to constrain the natural tendency to explore novel environments, revealed altered response inhibition in adolescent FAE rodents (112), particularly in female offspring (113). Further, both adolescent and adult FAE rats display a hyper-active/hyper-exploratory phenotype, including increased

nose-poking, head-dipping and locomotion (114) together with spatial perseveration in a Morris Water Maze task (103). Importantly, similar deficits in response inhibition and perseveration are frequently observed in FASD patients (105) and typically treated by using ADHD psychostimulant medications (<https://www.cdc.gov/ncbddd/fasd/treatments.html#Medication>), highlighting both the construct and predictive validity of FAE animal models. These behavioral experiments suggest an alternative hypothesis to the hyper goal-directed idea described above. In fact, the enhanced operant responding and inflexibility traits might derive from an inability of FAE to generate appropriate behavioral inhibition, which could further preclude the formation of novel behavioral patterns upon changes in external circumstances. Thus, considering that different corticostriatal circuits contribute to these different aspects of executive function, we speculate that FAE-induced impairments in those pathways lead to cognitive function deficits.

Corticostriatal pathways control action strategy and cognitive flexibility

The neuronal network connecting different neocortical areas to the striatum, which is part of a subcortical group of nuclei collectively known as the basal ganglia, constitutes the cortico-striatal pathways (115,116). In particular, neocortical areas send excitatory projections to the main class of neurons populating the striatum: the medium spiny neurons (MSNs; **Figure 2a**) (117). MSNs cluster in direct (projecting to the substantia nigra reticulata) and indirect (projecting to the globus pallidus) pathways, expressing dopamine 1 (D1R) or 2 (D2R) receptors, respectively (118). The neuromodulator dopamine, which is released by midbrain neurons, controls both the activity and synaptic plasticity at cortical inputs onto MSNs (119–121). MSNs regulate locomotion (122), action selection (123), goal-directed behavior and habit formation (106), all behavioral aspects altered by FAE. In particular, the reciprocal loops between associative and sensorimotor cortical areas to dorsal striatal regions (caudate and putamen) instruct the acquisition and performance of behavioral strategies (124,125). Goal-directed behavior, which drives the execution of an action to obtain a predicted outcome (also known as action-outcome strategy), relies on the function of the projections from associative (frontal) cortices, including the orbitofrontal (OFC) and the prefrontal cortex (PFC), to the dorsomedial striatum (DMS) (125,126). Habitual behavior, which consists of more automatized actions triggered by external stimuli and reinforcement history (stimulus-response actions), relies on the projections from sensorimotor cortices, including the primary motor cortex (M1), to dorsolateral striatum (DLS) (125,126). Action-learning rapidly engages the PFC-DMS (associative) pathway, which is disengaged as learning proceeds (124). At the same time, M1-DLS pathway activation increases as the action execution becomes habitual (127). Thus, a dynamic engagement of these pathways occurs during the performance of everyday actions and its perturbations might lead to psychiatric disorders characterized by the loss of inhibitory control and altered habit formation, both traits displayed by FASD patients. Moreover, cognitive flexibility, defined as the ability to disengage from habitual responding and

adapt action performance in the face of changing circumstances, relies on an intact functionality of OFC-DMS circuits. In fact, OFC neurons track the value of a stimulus (128) and update novel cue-reward contingencies (129). Thus, specific deficits in cortico-striatal networks might underlie the disrupted executive function capabilities of both in FASD patients and pre-clinical models of FAE.

An imbalanced cortical excitation/inhibition ratio

Evidence of cortical thinning in pre- (motor) and post- (somatosensory) central areas and frontal lobes (130,131), which encompass both the OFC and the PFC, support the hypothesis that altered cortico-striatal networks impair executive function in FASD patients. Additionally, children and adolescents affected by FASD present connectivity dysfunctions in sensorimotor networks (132). Similarly, FAE rodents show neuroanatomical, cellular and functional alterations in OFC, PFC, somatosensory cortex, motor cortex and striatum from infancy to adulthood (133–136). Because of the role of frontal cortex in learning and behavioral flexibility (137), several studies investigated the function of excitatory and inhibitory neurons in PFC of FAE rodents. In the PFC, developmental alcohol exposure decreases spine

Figure 2. Excitatory/inhibitory imbalance and corticostriatal pathway dysfunctions following FAE. (a) Schematics of neocortical neurons projecting onto striatal regions to control the recruitment of downstream striatal MSNs. (b) FAE alters the excitatory/inhibitory (E/I) balance within cortical regions to increase the excitability of projecting neurons. The increased functional connectivity between cortical and striatal regions might then result in synaptic potentiation and aberrant recruitment of striatal neuron ensembles.

density in layer II/III neurons (138) but enhances AMPAR function in pyramidal neurons of deeper cortical layers (96), which in turn send inputs to striatal regions (117). In Layer V/VI of the somatosensory cortex, an increase in both miniature and spontaneous excitatory post-synaptic currents (EPSCs), together with presynaptic facilitation, point to an increased excitatory drive on cortico-striatal neurons (135).

In parallel, FAE alters the tangential migration of developing cortical GABAergic neurons (139) and alters their number in their target cortical areas (140–142). Interestingly,

similar deficits in interneuron function contribute to the impaired excitation/inhibition balance (E/I) in animal models of autism (143) and might ultimately disrupt cortical neuron output in FAE offspring as well (**Figure 2b**). Corroborating evidence shows heightened coherence and hyper-excitability of piriform cortex-hippocampal networks upon cue-presentation, which seems to rely on aberrant excitatory synapse facilitation (144,145). Similarly, FAE mice display enhanced functional connectivity between OFC and striatum during specific phases of reversal learning (146). It should be noted that FAE increases both the number of Calretinin-positive GABAergic interneurons and the amplitude of inhibitory post-synaptic currents in the OFC (147), highlighting potential differences in the effects of EtOH based on the timing of the exposure and the brain areas analyzed. Thus, the hypothesis of an impaired cortical E/I balance and its effects on downstream striatal neurons needs to be further explored and requires careful consideration of the FAE model and brain area analyzed.

Corticostriatal miswiring

The formation of cortico-striatal networks is a controlled sequence of embryonic and postnatal events, which starts with the invasion of the embryonic striatum (E12-E13) by cortical projection axons and terminates with the completion of synaptic maturation around P30 (148). Exposure to alcohol interferes with these processes, leading to cell loss, reduced dendritic complexity, decreased neuronal excitability, altered neuromodulation and impaired synaptic transmission. In particular, EtOH exposure during development reduces the size of the caudate nucleus in humans (71,149) and a single EtOH injection during striatal synaptogenesis induces extensive apoptosis in the caudate-putamen striatal regions in mice (150). Moreover, FAE induces a significant reduction in dendritic complexity of GABAergic interneurons (151), which might also contribute to the reduced local GABAergic neuron function (107). EtOH exposure during pregnancy increases dendritic length (152) and produces sexually-dimorphic excitability deficits (153) in MSNs of the nucleus accumbens/ventral striatum. In the DMS, a striatal subregion functionally innervated by associative cortical inputs (127), FAE increases neuronal dendritic length, as well as amplitude and frequency of mEPSCs in direct pathway MSNs (154). In DLS, which is part of sensorimotor cortico-striatal loops (127), adolescent male offspring of ethanol-fed rat dams display heightened excitatory inputs and glutamate release probability (155). Moreover, FEA attenuates HFS-induced long-term potentiation (LTP) at cortico-striatal inputs during early adolescence, but promotes LTP at later stages of development, when HFS typically induces long-term depression (LTD) (155). Interestingly, D2R agonist application rescues HFS-induced LTD suggesting that FAE might promote aberrant forms of cortico-striatal maturation *via* dopamine signaling alterations.

Indeed, exposure to alcohol during development has been shown to impair dopamine signaling in the striatum, which can further contribute to corticostriatal input impairments. In monkeys, early and late

gestational ethanol exposure decreases and increases striatal dopamine function, respectively (156). In rodents, FAE decreases the expression of D2R during adolescence but it also reduces D1R during both adolescence and adulthood. These effects are associated with diminished dopamine transporter function to decrease dopamine re-uptake and exacerbate the behavioral adaptations induced by psychostimulant exposure later in life (157). Moreover, those dopaminergic impairments seem to contribute to hyperactivity (158), a behavioral trait commonly observed in both FASD and ADHD patients. Finally, since dopamine has been shown to control corticostriatal input formation, maturation (120) and plasticity (121), dopaminergic deregulation might further contribute to the corticostriatal excitatory synaptic deficits observed in FAE mice.

The data described above corroborate the idea of FAE-induced enhancement of excitatory transmission and plasticity at corticostriatal synapses. Appropriate synaptic plasticity at different corticostriatal inputs underlies multiple aspects of behavior, including goal-directed (159) and habitual (160) processes, and it has been hypothesized to control the recruitment of neuronal clusters (or neuronal ensembles) to promote behavioral output (123). Thus, despite the cell loss due to apoptotic processes, the increased excitatory transmission, the loss of GABAergic function and the impaired dopamine signaling might increase the recruitment of striatal neuronal ensembles and alter behavioral responses in FAE mice (**Figure 2b**). Because the various corticostriatal loops control different aspects of action selection and performance, the elucidation of the FAE-induced neuronal defects occurring in discrete corticostriatal networks might help to establish a causal link between circuits and cognitive impairments.

Model 1: Associative-sensorimotor imbalance

A model of striatal action selection posits that a “go-circuit” might engage an associative pathway (OFC-DMS) during goal-directed actions (e.g. learning) and sensorimotor (M1-DLS) circuits during habitual behaviors (**Figure 3**). Thus, positive reinforcers would activate a goal-directed “go-circuit” and changes in outcome value would modulate its activity. The habitual execution of an action would instead recruit sensorimotor circuits and be less sensitive to changes in outcome value. In fact, impairments of the OFC-DMS (associative) pathway disrupt goal-directed behavior in favor of an over-reliance on habitual responding, which is insensitive to outcome devaluation (106,159,161). Accordingly, activation of the OFC-DMS pathway promotes goal-directed behavior (159) while motor stereotypies rely on an increased functionality of motor areas in motor diseases (162). It has been shown that the FAE-induced enhancement of operant responding depends on a decreased function of parvalbumin-positive GABAergic interneurons (107), which leads to hyperexcitable MSNs in sensorimotor DLS (red square in **Figure 3**). However, while chemogenetic activation of parvalbumin-positive GABAergic interneurons in DLS rescued the enhanced lever-pressing behavior and decreased MSN firing of FAE mice, it did not ameliorate habit formation

Figure 3. Model 1 of associative-sensorimotor imbalance. The associative-sensorimotor imbalance model posits that FAE promotes hyper goal-directed behavior; while the enhanced lever-pressing behavior derives from hyperfunctional sensorimotor pathway (S1/M1-DLS), the impaired habit formation and behavioral flexibility are due to a hyperactive associative pathway (OFC-DMS).

impairments (107). This suggests that, while enhanced lever pressing derives from dysfunctional sensorimotor loops, habit formation deficits might originate from associative corticostriatal impairments. In particular, we hypothesize here that an “associative-sensorimotor imbalance” might underlie impaired habit formation, whereby the hyperactivation of OFC-DMS pathway biases towards goal-directed strategies and destabilizes automatized patterns of responding (**Figure 3**). Importantly, this model works with the assumption that while both pathways might be hyperfunctional, the net increase in associative corticostriatal network function prevails over potentiated sensorimotor pathways. This idea is corroborated by the evidence that repeated optogenetic stimulation of OFC-ventromedial striatum also promotes action repetition (163). In an animal model of OCD (knock-out for *Sapap3*), habit formation has been studied by developing a learning task of cue-induced self-grooming behavior (164). While cue-induced anticipatory grooming disappeared in WT mice, it was retained by *Sapap3* KO mice and indicated a higher vulnerability to develop habits. This behavioral impairment was associated with higher activation of striatal neuron activity. Importantly, enhancing feed-forward inhibition

on MSNs *via* lateral OFC stimulation ameliorated compulsive grooming. Thus, this data further indicate that associative pathway activation prevents the expression of aberrant habitual behavior.

As described above, EtOH exposure during brain development profoundly impacts behavioral flexibility, which also relies on the intact functionality of corticostriatal associative pathway. In fact, neuronal impairments in both OFC and DMS affect reversal learning in humans, primates and rodents (24,137,165,166). While hypoactivation of OFC characterizes deficits in reversal learning in animal models of OCD (167), recent data suggest that synaptic strengthening and weakening of secondary motor cortex and OFC striatal inputs, respectively, contribute to compulsive behavior in a model of OCD (168). Further, the OFC-striatal associative pathway is hyperactive during specific phases of a reversal-learning task in FAE offspring (146). This evidence supports the idea that hyperactive associative pathways would not only

impede habit formation, but the enhanced goal-directed behavior would also interfere with the formation of novel action-outcome associations, thus resulting in cognitive flexibility impairments (**Figure 3a**). Chemogenetic and optogenetic experiments in FAE mice will further clarify the contribution of imbalanced function of associative and sensorimotor striatal circuits to the aberrant operant responding, habit formation and behavioral inflexibility in preclinical models of FASD.

Model 2: Impaired prefrontal-striatal suppression circuits

Suppression (or inhibition) of behavioral responses is a fundamental aspect of executive function. To obtain a desirable outcome under given circumstances, individuals need to select a defined behavioral program (23), which requires the suppression of neurobehavioral processes that might interfere or compete with the execution of that particular action. The inability to inhibit motor or cognitive programs is a hallmark of action repetition in several neuropsychiatric disorders, including OCD (169) and addiction (170). As described above, FASD symptoms share some traits with those diseases, as evidenced by the enhanced operant responding, behavioral inflexibility and addiction vulnerability following FAE (105). Although the discussion of the behavioral roles of the different prefrontal cortex (PFC) subdivisions and their projection targets goes beyond the scope of this review, it is important to recognize that the medio-lateral and dorso-ventral PFC control different aspects of behavioral execution (171,172). Inactivation studies indicate that the prelimbic and infralimbic PFC subregions are necessary to suppress premature and nonspecific actions in instrumental tasks or inhibit behavioral responses in go/no-go tasks (173–177). Moreover, human imaging studies reported impaired fronto-striatal network activity during behavioral inhibition tasks in both ADHD and FASD patients (178,179). Inactivation studies further indicate that the PFC is necessary for appropriate reversal learning upon cross-modality changes (180–182), most likely by suppressing either obsolete action-outcome associations and/or actions dictated by previously learned sets of rules. Altogether, these studies support a second model by which an FAE-induced dysfunctional prefrontal-striatal pathway impairs behavioral suppression and results in operant responding and flexibility defects (**Figure 4**). Assessing resistance to punishment (or compulsivity) as a metric of perseverative and inflexible behavior would be interesting to probe the function of prefrontal-striatal networks in FAE mice. In fact, compulsive behavior seems to originate from hypofunctional prefrontal-striatal inhibitory circuits (183), which are normally recruited when an aversive stimulus (*e.g.* foot-shock) is paired with cocaine administration to discontinue drug-taking.

Recent data indicating that a potentiation of prefrontal-striatal inputs enhances operant responding in animal models of compulsivity challenge this second model. In fact, cocaine-withdrawal potentiates PFC-NAc inputs to drive cocaine-seeking (184) and strengthening or depressing prefrontal-striatal pathway increases and decreases alcohol-seeking (185), respectively. However, we should note that different

subregions of the PFC (dorsal *vs* ventral) play different roles in compulsivity and their manipulations might either enhance or suppress drug-taking depending on the behavioral paradigm (172).

Model 2 Impaired prefrontal-striatal suppression circuit

Figure 4. Model 2 of impaired prefrontal-striatal suppression circuits. The prefrontal-striatal suppression circuit model posits that a dysfunctional PFC-striatal pathway fails at suppressing behavioral responding, resulting in enhanced lever-pressing. It also implies that the inability to suppress previously learned action-outcome associations results in behavioral inflexibility when novel action-outcome associations are needed.

It should also be noted that this second model does not necessarily require functional impairments in associative or sensorimotor pathways. In fact, deficits in the PFC-striatal loop might result in the failure to suppress behavioral programs that originate from associative and sensorimotor inputs but are not normally engaged. Other than PFC, OFC-striatal pathways have also been implicated in behavioral response inhibition. For example, depotentiation of OFC-DMS inputs reduced compulsive DA neuron-self stimulation in a model of reward-seeking despite punishment (186) and self-grooming is inhibited by OFC neuron stimulation *via* reduced MSN activity (164). Thus, we believe that the elucidation of the defects in cortico-striatal inhibitory circuits following FAE is of paramount importance to better understand the circuit defects underlying the perseverative behaviors and the impaired reversal learning following FAE.

Model 3: Striatal output pathway deficits

A third and alternative model that could explain the behavioral deficits induced by FAE entails a disruption of striatal output pathway activity to impair executive function (**Figure 5**). It has been proposed

Figure 5. Model 3 of striatal output ensemble deficits. The striatal output deficit model implies that local striatal dysfunctions might induce an aberrant recruitment of striatal MSN ensembles. The heightened excitability of direct pathway MSNs would prevail upon indirect pathway inhibitory signals to strengthen action-outcome associations and increase action repetition (e.g. lever-pressing). Additionally, the increased striatal ensembles would preclude the formation of other MSN ensembles that would encode novel action-outcome associations thus resulting in behavioral inflexibility.

and discussed elsewhere (123) that discrete ensembles of striatal neurons control learning and execution of specific actions. While early studies proposed a go/no-go model whereby direct and indirect MSNs have opposing roles in behavioral execution (187,188), recent *in vivo* studies indicate that increased activity in both striatal output pathways determines the selection of an appropriate action (189). To reconcile these apparently conflicting models, we hypothesized that the balance between go and no-go signals, respectively encoded by direct and indirect MSNs

within a discrete striatal ensemble, determines the execution of an action (123). According to this idea, the enhanced lever pressing behavior observed during RR training of FAE mice (107) might be mediated by an exaggerated recruitment of direct MSNs within a given striatal ensemble (**Figure 5**). Direct MSN hyperactivity would largely prevail on the inhibitory function of indirect MSNs resulting in aberrant repetition of the same action. Moreover, the FAE-induced dysfunctions in reversal learning might reflect dysfunctional recruitment of novel striatal ensembles to update striatal output information and allow new behavioral patterns to stabilize (**Figure 5**). The evidence that an endocannabinoid-mediated reduction in local GABAergic tone enhances MSN excitability in DLS (107), possibly deregulating striatal neuron

ensemble function, further corroborates this idea. Finally, the role of dopamine in controlling both the recruitment of MSN ensembles (190) and the synaptic plasticity at lateral inhibitory synapses between MSNs (191,192) suggests that a deregulated dopamine signaling might also impair the local GABA-mediated control of striatal output function following FAE.

Altogether these data strengthen the idea that FAE-induced executive function deficits originate from complex interactions between corticostriatal input, dopaminergic and GABAergic signaling impairments to recruit aberrant striatal neuron ensembles. Single-cell recordings and calcium imaging experiments in medial and/or lateral striatal subdivisions together with cortical input manipulations will help to clarify the contribution of each corticostriatal pathway to the FAE-induced behavioral symptoms. The identification of abnormal brain circuits will then allow a mechanistic approach to test the efficacy of drugs and other neuronal circuit manipulations to ameliorate the cognitive impairments induced by FAE.

Preclinical interventions for FAE-induced behavioral dysfunctions

Although the CDC describes FASD as a chronic and untreatable disorder, some medications seem to ameliorate specific neurobehavioral symptoms. In fact, despite variable outcomes (6,193), psychostimulant drugs used for ADHD treatment ameliorate hyperactivity and attention deficit symptoms of FASD patients. However, while very few clinical studies have focused on finding novel therapeutic options for FASD (194), there is a large body of preclinical literature focused on preventing, ameliorating and/or rescuing cognitive deficits induced by FAE (6). Here, we review some of the pre-clinical studies that provided a neurobiological mechanism underlying the behavioral benefits following drug administration. Based on the timing of intervention, we propose a distinction between: (A) protective treatments that overlap with fetal EtOH exposure to prevent FAE symptoms; (B) restorative strategies that begin after the onset and throughout EtOH exposure and early postnatal periods, to attenuate or rescue neurobehavioral impairments; and (C) acute options, which consist in brief treatments during adolescence and adulthood, once brain maturation is complete (**Figure 6**). In the first category, the polyphenol flavonoid dihydromyricetin prevents the alcohol-mediated enhancement of GABA_AR function and protects against some of the FAE-induced behavioral dysfunctions (195), thus opening the possibility of natural supplementation use for FASD prevention. Similarly, when co-administered with EtOH at early postnatal stages, lithium prevents neurodegeneration, hippocampal LTP deficits and aberrant cortical paired-pulse facilitation (145).

Figure 6. Potential therapeutic approaches for neurobiological and behavioral dysfunctions in pre-clinical models of FAE. Based on the timing of intervention, the therapeutic approaches can be divided into protective, which overlaps with FAE, restorative, which partially overlap but are often protracted beyond FAE and acute, which involves the administration of the treatment after the end of the FAE (typically starting during adolescence or adulthood).

Among the restorative interventions, thyroxine (a thyroid hormone) and metformin (a drug used in Diabetes type II to lower blood glucose) neonatal treatment (corresponding to the last trimester of human pregnancy) restore hippocampal gene-expression and ameliorate deficits in both spatial and fear learning in the adult FAE offspring (196,197). This drug regimen would counteract the hypothyroidism and increased glucose levels induced by EtOH consumption during pregnancy

and is supported by the evidence that reduced levels of thyroid hormones disrupts LTP in neonatal mice (198,199). Other restorative treatments include the administration of a neural plasticity enhancer, vinpocetine (a phosphodiesterase type I inhibitor), which restores ocular dominance plasticity in a ferret model of FAE (200), or choline supplementation during early postnatal days, which promotes both spatial learning and behavioral flexibility in FAE adolescent offspring (201–203). Although the mechanisms of action of choline supplementation remain unclear, choline is a precursor of the neuromodulator acetylcholine. Among other functions, acetylcholine (ACh) controls dopamine release *via* activation of muscarinic and nicotinic receptors onto pedunclopontine afferents or striatal pre-synaptic dopaminergic terminals (204). Importantly, acetylcholine-mediated dopamine release is an important regulator of corticostriatal plasticity (205). Thus, an intriguing hypothesis is that choline might promote acetylcholine production, which in turn could modulate and normalize dopamine release and regulate dopamine-dependent corticostriatal plasticity in FAE mice.

Acute treatments for FAE-induced deficits include the administration of the cognitive enhancer ABT-239 (a histamine receptor 3 antagonist), which ameliorates fear learning and spatial memory defects as well as altered LTP induction in the dentate gyrus of FAE offspring (206,207). The neuroprotective peptides NAP (NAPVSIPQ) and SAL (SALLRSIPA), which demonstrated brain permeability upon intranasal or systemic injections (208), appear to protect against learning impairments (209) and NMDAR subunit composition deficits (210) in FAE rodents. More recently, it has been shown that a 10-day long NAP and SAL treatment during adolescence also rescues spatial learning and restores appropriate NMDAR subunit composition in the hippocampus, neocortex and cerebellum of FAE offspring (211). Aniracetam, a nootropic enhancer of AMPAR function, administered for 10 days during adolescence reduced anxiety,

improved learning and rescued the reduced AMPAR current frequency and amplitude in a rat model of FAE (212). Altogether, these data suggest potential therapeutic use of these compounds later in life. Finally, non-pharmacological interventions, including physical activity or brain stimulation might be effective in rescuing FASD cognitive deficits. For example, it has been shown that voluntary exercise during late adolescence improves spatial memory as well as LTP deficits in the dentate gyrus of FAE offspring (213). In recent years, the improved understanding of brain circuit dysfunctions underlying specific behavioral impairments led to the establishment of targeted brain stimulation protocols to ameliorate symptoms of several neuropsychiatric disorders, including Parkinson's disease (214), drug-addiction (215), depression (216). Interestingly, most of the deep-brain stimulation (DBS) or transcranial magnetic stimulation (TMS) paradigms focused on cortico-striatal circuits and appeared to be effective in rescuing neuronal circuit deficits as well as some of the neurobehavioral symptoms shared with FASD. Recently, a double-blind randomized study reported that transcranial direct current stimulation of dorso-lateral PFC improved attention upon continuous training to enhance cognitive function in FASD children (217), demonstrating both the safety and the efficacy of targeted neural stimulation in young patients. While this clinical study represents an important step in developing novel therapeutic options for FASD, pre-clinical studies will be instrumental for elucidating the effects of drugs or circuit stimulation on cortico-striatal function to provide a mechanistic understanding of the neurobiological effects of those treatments in humans.

Conclusions

The cognitive impairments associated with FASD negatively impact patient everyday life resulting in high societal and economic burden. The lack of knowledge about brain circuits related to those symptoms has slowed progress towards the development of effective therapeutic strategies. Here, we discussed three models of cortico-striatal circuit dysfunctions that could account for the executive deficits observed in FASD preclinical models. A better understanding of neuronal deficits underlying those behavioral impairments will enormously benefit the development of effective therapeutic interventions for FASD patients. Different techniques enable precise circuit dissection of brain deficits in animal models of psychiatric disorders; slice physiology (*ex vivo*) recordings can help to clarify the role of synaptic and neuronal excitability in cortical and striatal regions, while *in vivo* electrophysiology can provide useful insights on the FAE-induced functional impairments of cortical or striatal neurons in behaving animals. The use of optogenetic techniques allows a powerful dissection of input-output circuit dysfunctions. Additionally, imaging calcium transients as a proxy for neuronal activity in large neuronal cellular populations can provide a better understanding of the FAE effects on the recruitment of striatal neuron ensembles. After the careful dissection of circuit dysfunctions, chemogenetic and optogenetic approaches could be applied to rescue aberrant neuronal activity in defined brain regions to ameliorate, for example, discrete executive function

deficits. These approaches will help to tailor precise translational approaches to defined brain circuits and to understand which dysfunctional aspects of circuit physiology (e.g. loss of synaptic plasticity, enhanced excitability, imbalanced pathway function and/or altered neuronal ensemble recruitment) need to be ameliorated to obtain effective rescue strategies. These experiments would have particularly high translational value because they can be used to target other FASD traits, such as socio-emotional dysfunctions, and/or similar neurobehavioral symptoms of other neuropsychiatric disorders.

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