Corticostratial Circuit Models of Cognitive Impairments Induced by Fetal Exposure to Alcohol

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ABSTRACT
The term fetal alcohol spectrum disorder includes a group of diseases caused by fetal alcohol exposure (FAE). Patients with fetal alcohol spectrum disorder display heterogeneous socioemotional and cognitive deficits, particularly in the domain of executive function, that 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 effects of FAE on corticostratial development and its impact on both corticostratial pathway function and cognitive abilities. We propose three non–mutually exclusive circuit models of corticostratial 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 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 preclinical approaches applied to these circuit models could offer potential rescue strategies for executive function deficits in patients with fetal alcohol spectrum disorder.

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The teratogenic effects of ethanol (EtOH) manifest as prevalent and heterogeneous somatic abnormalities as well as lifelong neurobehavioral deficits, collectively known as fetal alcohol spectrum disorder (FASD) (1–4). Despite an estimated prevalence of 0.3–0.8 per 1000 children (1,5) and a yearly economic burden of about $4 billion (6), precise brain circuit-based therapeutics for FASD remain unexplored. Rodent models of FASD have been developed to investigate synaptic impairments in brain regions involved in socioemotional and motor deficits (7). Here, we focus on the effects of fetal alcohol exposure (FAE) on the neocortex and striatum, because of their vulnerability to the teratogenic effects of alcohol (8) and their role in executive function, which is severely compromised in individuals with FASD. We propose 3 non–mutually exclusive models of corticostratial circuit impairments that might account for FASD cognitive deficits. The first model involves imbalanced function of associative-sensorimotor pathways, the second entails deficits in behavioral inhibitory circuits, and the third focuses on striatal output dysfunctions. Finally, we discuss potential therapeutic strategies in the framework of the proposed FAE circuit models.

COGNITIVE DEFICITS CAUSED BY FETAL EXPOSURE TO ALCOHOL
FAE impairs both socioemotional processes (9) and executive functions, which are a set of cognitive abilities available to an individual to execute an action and/or reach a desired goal (10). They include attention, learning and retention of cue and action-outcome associations, generation of goal-directed behaviors via action selection, and inhibition of competing behavioral patterns. Once learned, behavioral responses become automatized or habitual. This allows for the formation of novel action-outcome associations and behavioral adaptations in the face of changing circumstances (11), a process described as cognitive flexibility. FAE impairments threaten spatial working memory (12), action planning (13), and intelligence quotient (14); leads to hyperactivity (15); and compromises response inhibition (16,17). Children (18) and adults (19) with FASD display deficits in response extinction (20), cognitive flexibility, and specific learning aspects, such as memorization (21) and declarative, rather than procedural, memory (22).

The cognitive and socioemotional deficits observed in patients with FASD often resemble symptoms of other neuropsychiatric disorders (23) and can confound the FASD diagnosis (24). In this framework, the use of animal models of FASD might help to clarify the neuronal circuit deficits induced by FAE but also other neuropsychiatric disorders. A similar approach can be applied to the identification of circuit-based rescue strategies for cognitive and socioemotional deficits of FASD animal models.

RODENT MODELS OF FASD
FAE can alter various stages of brain development (25). Some women unaware of their pregnancy consume large alcohol quantities in a limited time (binge-drinking), and 87% of them...
Table 1. Analogies of Executive Function Deficits Between FAE Rodent Models and Patients with FASD

| Behavioral Deficit            | FAE Paradigm                                      | Blood Alcohol Concentration | Behavioral Task                  | Age         | Sex       | References                      | Examples of Behavioral Correlates in Humans |
|-------------------------------|---------------------------------------------------|-----------------------------|----------------------------------|-------------|-----------|---------------------------------|-------------------------------------------|
| Reduced Attention             | Sprague Dawley rats, E(GD)8-E20, intragastric intubation, 6 g/kg daily | E20: 281–341 mg/dL          | CRT task                         | Adult<sup>a</sup> | Male only | Hausknecht et al., 2005 (36)   | CANTAB (12)                               |
| Low Accuracy/Increased Omissions | C57BL/6J mice, oral gavage E10-E18 (2-4 g/kg daily) and P4-P14 (1.5-3 g/kg daily) | E15: 234.8 ± 34.2 mg/dL, P10: 255.2 ± 43 mg/dL | Five-choice serial reaction time task | P60         | Male only | Louth et al., 2016 (37)        | CANTAB (12)                               |
| Spatial Working-Memory Deficits | Pigmented Long-Evans rats, P6-P9, gastrotomy, 6 g/kg daily | P9: 301.7 ± 16.8 mg/dL      | Delayed matching-to-place task   | P35, P105, and at >6 mo | Male only | Girard et al., 2000 (38)       | CANTAB (12)                               |
| Increased Operant Responding for Alcohol | Wistar rats, intragastric intubation, E17-E20, 1-2 g/kg daily | Dams: 50–160 mg/dL<sup>b</sup> | Neonatal operant conditioning    | P1          | Male and female | March et al., 2009 (39), Dominguez et al., 1996 (144) | SUD vulnerability (44) |
| Increased Operant Responding for Cocaine | C57BL/6, limited access to 20% EtOH, 4 days/wk, E0-P21 | E21/P21: approx. 80 mg/dL   | Conditioned place preference, cocaine self-administration | Adults     | Male only | Cantacorps et al., 2020 (42) |                                          |
| Increased Operant Responding for Amphetamine | Sprague Dawley rats, intragastric intubation, E8-E20, 3-4 g/kg daily | Dams: 281–341 mg/dL<sup>b</sup> | Amphetamine self-administration | 8 weeks     | Male only | Hausknecht et al., 2015 (41), Choong and Shen, 2004 (145) |                                          |
| Reduced Extinction for EtOH    | Sprague Dawley rats, intragastric, single dose of 1 g/kg dose between E17-E20 | Dams: approx. 50 mg/dL<sup>b</sup> | Neonatal operant conditioning    | P5          | Male and female | Miranda-Morales et al., 2014 (40), Dominguez et al., 1996 (144) | Extinction test (20) |
| Enhanced Reinstatement        | C57BL/6J mice, limited drinking access between E0-E21, 3-4 g/kg in 4 hours to 0 until P6 | Dams: approx. 80-90 mg/dL   | Operant conditioning (touchscreen)<sup>c</sup> | 2 mo        | Male and female | Olguin et al., 2019 (46) | SUD vulnerability<sup>‡</sup> (44) |
| Impaired Habit Formation      | C57BL/6J mice, CIE, E0-P10                          | Dams: approx. 80 mg/dL      | Random ratio/random interval training followed by outcome devaluation test | 2–3 mo      | Male and female | Cuzon Carlson et al., 2020 (45) | Poor action planning (13) |
| Impaired Reversal Learning    | Sprague Dawley rats, P4-P9, intragastric intubation, 5 g/kg daily | P4: 320 ± 7 mg/dL           | T-maze                           | P28         | Male<sup>c</sup> | O’Leary-Moore et al., 2006 (49) | WCST (13)                                |
|                              | C57BL/6J mice, limited drinking access between E0-E21, 3-4 g/kg in 4 hours to 0 until P6 | Dams: approx. 90 mg/dL      | Y-maze                           | P40–P50     | Male only | Allan et al., 2014 (47)        |                                          |
stop drinking after pregnancy has been ascertained (26). While repeated and binge-like EtOH exposures are the most detrimen
tal (27), it has been increasingly recognized that there is no safe amount of alcohol in pregnancy. Thus, preclinical re
searchers need to carefully consider the dose and the timing of EtOH exposure and draw meaningful parallels between pre
clinical and clinical neurobehavioral deficits. In rodents, EtOH ingestion can be achieved by voluntary drinking of a sweet
ened ethanol-containing solution before and during gestation (28) or by feeding dams with an ethanol-enriched liquid diet
(29). Consumption of EtOH that results in exposure to low-
moderate blood levels (28) occurs in 53% of pregnant women who continue drinking throughout pregnancy (26). While
drinking does not allow tight control over blood alcohol concentra
tion, intraperitoneal injections (30) or intragastric intu
bation (31) induce a reliable binge-like circulating alcohol surge in rodents (blood alcohol concentration > 200 mg/dL). These methods are useful to mimic either isolated or repeated binge-
like drinking episodes, which occur in about 18% of women unaware of their pregnancy and in 39% of women who continue to drink throughout pregnancy (26). However, injec
tions are not the typical route of exposure and might lead to nonphysiological increases of ethanol in fetal circulation (32).
Similarly, intubation negatively affects the dam’s well-being, especially if protracted over time. A relatively easy preclinical FASD model is the cyclic exposure to and withdrawal from EtOH vapor (33), which leads to stable and high blood alcohol concentration (above 175 mg/dL; peak at 200 mg/dL) (34). This method requires minimal handling and no injections, intuba
tion, or maternal separation of neonatal rodents to mimic the 27% of EtOH exposures that protract into the third gestational trimester (26,35). In contrast, inhalation is not the usual route of alcohol consumption and might irritate the respiratory tract (32), which could in turn act as a stressor. Although each of

Table 1. Continued

| Behavioral Deficit | FAE Paradigm | Blood Alcohol Concentration | Behavioral Task | Age | Sex | References | Examples of Behavioral Correlates in Humans |
|--------------------|--------------|-----------------------------|----------------|-----|-----|------------|-------------------------------------------|
| Sprague Dawley rats, isocaloric EtOH diet, E0–E21 | E16: 116.98 mg/dL | Go/no-go task (auditory discrimination) | P90 | Male only | Mihalick et al., 2001 (50) | WCST (13) |
| CS7BL/6J mice, limited drinking access between E0–E21, 3–4 g/kg in 4 hours to 0 until P6 | Dams: 88.3 ± 11.5 mg/dL | Operant conditioning (touchscreen) | 8–14 weeks | Male only | Marquardt et al., 2020 (101), Brady et al., 2012 (146) | WCST (13) |
| Perseverative Traits | Long-Evans rats, limited drinking access to 5% EtOH, 2.72 g in 4 hours, E0–E21 | Dams: 84.0 mg/dL | Morris water maze | 4–11 mo | Male only | Hamilton et al., 2014 (43), Savage et al., 2010 (147) | WCST (13) |
| Decreased Response Inhibition | Long-Evans rats, isocaloric diets, 0%, 17%, or 35% EtOH, E6–E16 | E15 for 17%: 0.02% | Passive avoidance task | P18 and P41–P53 | Male and female | Riley et al., 1979 (51) | Delis-Kaplan Executive Function Scale (16) |
| | | E15 for 35%: 0.25% | | | | | |
| | Long-Evans rats, intragastric intubation, 6 g/kg daily, P4–P10 | P6: 373 ± 74 mg/dL | Passive avoidance task | P23 | Female | Barron and Riley, 1990 (52) | |
| Hyperactivity | Long-Evans rats, isocaloric diets, 0%, 11%, 23%, or 35% EtOH, E5–E20 | E10–E15 for 11%: 0.03% | Nose-poke or head-dipping exploratory behavior | P29–P34 | Male only | Riley et al., 1979 (53) | Hyperactivity (15) |
| | | E10–E15 for 23%: 0.06% | | | | | |

*Table reports the cognitive deficits observed in different preclinical models of FASD of different ages and sexes across diverse behavioral tasks. Some of these deficits have analogies with impairments in executive function observed during specific clinical tests conducted on patients with FASD.

BAC, blood alcohol concentration; CANTAB, Cambridge Neuropsychological Test Automated Battery; CIE, chronic intermittent ethanol exposure; CRT, choice reaction time; E, embryonic day; EtOH, ethanol; FAE, fetal alcohol exposure; FASD, fetal alcohol spectrum disorder; P, postnatal day; SUD, substance use disorder; WCST, Wisconsin Card Sorting Test.

*BAC not reported in this study but based on previous publications using the same FAE model (144–147).

*This study did not use a drug reward, but reinstatement of responding might be a component of SUD vulnerability.

*Deficits not observed in the opposite sex.
these EtOH exposure protocols needs careful consideration, they have all provided useful preclinical models to study FAE-induced behavioral and circuit deficits.

**EXECUTIVE FUNCTION DEFICITS INDUCED BY FETAL ALCOHOL EXPOSURE IN RODENTS**

Animal models of FAE display executive function deficits analogous to those observed in individuals with FASD (Table 1). For example, attention deficits in adult rats with FAE have been reported as increased reaction times, augmented false alarm rates, and reduced response accuracy (36,37). Furthermore, in a delayed matching-to-place Morris water maze task, male rats with FAE performed poorly at longer, but not shorter, intertrial intervals (38). This evidence points to impaired spatial working memory but intact learning at sufficiently brief intertraining intervals. The effects of FAE on learning can also be studied throughout life, starting as early as postnatal day (P) 1 (39). Studies in which EtOH was provided as the outcome that produced positive reinforcement revealed increased acquisition and reduced extinction (39,40) of responding during infancy. Similarly, FAE increases operant responding for psychostimulants during adulthood (41,42), but it does not affect learning in other tasks (43). Thus, despite causing attention and working-memory deficits, FAE may increase reward sensitivity, allowing, and in some cases enhancing, reward seeking. It also appears that FAE might predispose to alcohol- and drug-seeking in rodents, traits resembling the highly prevalent substance use disorders (SUDs) observed in patients with FASD (44).

The FAE-induced enhancement of operant responding points to impairments in action strategy. In this context, we recently showed that mice with FAE increased lever pressing during training on a random ratio schedule and exhibited devaluation of responding, indicating appropriate use of a goal-directed strategy. However, these mice retained goal-directed behavior following random interval training, suggesting impaired habit formation (45). Other studies reported that maladaptive perseverative responses underlie inflexible behavior. In fact, in the absence of overt learning deficits, adult mice with FAE display enhanced reinstatement (46). Similar to deficits observed in individuals with FASD (44), these impairments are associated with altered behavioral flexibility in both adolescent and adult FAE offspring (7,47–50). 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, are intriguing. Would hyper goal-directed strategies based on previously learned action-outcome associations hinder the animal’s ability to update action-outcome associations?

Rodent models of FASD display reduced response inhibition (51), particularly in female offspring (52), hyperactivity, and spatial perseveration (43,53), all behavioral traits frequently observed in patients with FASD as well (44). Thus, the enhanced operant responding and inflexibility traits might instead derive from an inability of FAE offspring to generate appropriate behavioral inhibition and update action strategies.

The projections from the neocortex to striatum constitute different corticostriatal pathways. Within this review, we will refer to the primary somatosensory cortex (S1) and primary motor cortex (M1) as separate from the prefrontal cortex (PFC), which instead includes the orbitofrontal cortex (OFC; or lateral PFC) and the medial PFC (mPFC), the latter further subdivided into prelimbic (PL) cortex and infralimbic (IL) cortex (54). All these areas send excitatory projections to the main class of striatal neurons, the medium spiny neurons (MSNs) (Figure 1A) (55). MSNs contribute to direct (projecting to the substantia nigra reticulata) and indirect (projecting to the globus pallidus) pathways, expressing dopamine D1 or D2 receptors, respectively (56). The neuromodulator dopamine controls both activity and synaptic plasticity at cortical inputs onto MSNs (57). In turn, MSN output regulates locomotion, action selection, goal-directed behavior, and habit formation (58), all behavioral aspects altered by FAE. Thus, an appealing possibility is that FAE-induced behavioral deficits derive from aberrant development of corticostriatal pathways.

**THE TERATOGENIC EFFECTS OF ALCOHOL ON CORTICOSTRIATAL DEVELOPMENT**

FAE affects several stages of brain development (35), which ultimately impact corticostriatal circuits. While we recognize that glia may also contribute to FASD symptoms (59), our focus is on the neuronal changes induced by FAE. During early embryonic development (E0–E10), EtOH interferes with the function of proteins involved in neuronal proliferation and apoptosis, including glycogen synthase kinase 3β (60) and insulin-like growth factor (61). FAE also affects neuronal differentiation by deregulating doublecortin (62) and cAMP/CREB signaling pathways. Although these studies focused on the hippocampus, similar mechanisms might induce macroscopic deficits in the neocortex and striatum. In fact, FAE decreases thickness in motor, somatosensory, and prefrontal cortices (64,65); induces extensive apoptosis (66); and reduces the size of the caudate nucleus (67).

The assembly of corticostriatal pathways begins around E11–E13, when deep-layer cortical neurogenesis occurs and the pyramidal tract extends toward subcortical areas (68). By interfering with Src protein function, EtOH decreases dendrite growth (69), which might impair inputs onto corticostriatal neurons. In fact, FAE decreases spine density in layer II/III PFC neurons (70) but enhances AMPA receptor function in deep-layer pyramidal neurons (37), which project to the striatum. In S1 layer V/VI neurons, an increase in miniature and spontaneous excitatory postsynaptic currents, together with presynaptic facilitation, point to increased excitatory drive (71). In parallel, epigenetic dysfunctions induced by FAE-mediated MecP2 BDNF/DLX5 deregulation might alter GABAergic (gamma-aminobutyric acidergic) neuron tangential migration (35,72) to decrease their number in target cortical areas (73–75). Thus, similarly to the GABAergic-induced increase in excitation/inhibition balance (E/I) in animal models of autism (76), FAE might increase the E/I balance by increasing and reducing glutamatergic and GABAergic function, respectively (Figure 1B). However, contrasting evidence reported that FAE increases both the number of calretinin-positive GABAergic interneurons and the amplitude of inhibitory postsynaptic currents in the OFC (77). These data point to potential diverse FAE effects due to the brain region and timing of the exposure.
where the latter might contribute to the heterogeneity of FASD symptoms.

Around P3–P4, corticostriatal axons descend into the developing striatum \(78\), and alcohol exposure during this period, most likely via its actions on somatic GABA and NMDA receptors \(79\), induces extensive cortical apoptosis \(80\) and impairs callosal projections \(78,81,82\). Corticostriatal synapses develop between P1–P14 \(83\), while MSNs decrease their intrinsic excitability, reduce the kinetics of AMPA-mediated currents, and increase synaptic AMPA/NMDA ratio \(84,85\) during the following postnatal weeks. EtOH might alter these synaptic maturation processes by interfering with the expression of pre- and postsynaptic proteins, including synapsin, synaptotagmin, and MAP2 \(86\). In fact, FAE increases dendritic length \(87\) and produces sexually dimorphic excitability deficits \(88\) in MSNs of the nucleus accumbens within the ventral striatum. In the dorsomedial striatum (DMS), a striatal subregion innervated by associative cortical inputs \(89\), FAE increases dendritic length and amplitude and frequency of miniature excitatory postsynaptic currents in direct pathway MSNs \(90\). In the dorsolateral striatum (DLS), which is part of sensorimotor corticostriatal loops \(89\), adolescent male offspring display heightened excitatory inputs and glutamate release probability \(91\). Moreover, FAE attenuates high-frequency stimulation–induced long-term potentiation at corticostriatal inputs during early adolescence but promotes long-term potentiation at later stages of development, when high-frequency stimulation typically induces long-term depression \(91\). D₂ receptor agonist application rescues high-frequency stimulation–induced long-term depression, suggesting that FAE promotes aberrant forms of corticostriatal maturation via dopamine signaling alterations. Exposure to EtOH throughout or during middle-to-late gestation in monkeys decreases and increases striatal dopamine function, respectively \(92\). In rodents, FAE decreases D₂ receptor binding during early adolescence but reduces D₁ receptor binding during both early and late adolescence \(93\). These effects are associated with diminished dopamine transporter function \(93\) to decrease dopamine reuptake and exacerbate the behavioral adaptations induced by psychostimulant exposure later in life \(93\). Moreover, those dopaminergic impairments seem to contribute to hyperactivity \(94\), a behavioral trait commonly observed in patients with FASD. Because dopamine controls corticostriatal input formation, maturation, transmission, and plasticity \(57,95\), dopaminergic deregulation might further contribute to the corticostriatal excitatory synaptic deficits observed in mice with FAE. Finally, FAE induces a significant reduction in dendritic complexity of GABAergic interneurons \(96\), which might also contribute to reduced local GABAergic neuron function and increased MSN excitability \(45\).

Altogether, these data support the hypothesis that FAE aberrantly heightens corticostriatal circuit function via increased E/I ratio in cortical regions and potentiation of cortical inputs onto striatal neurons (Figure 1B). This idea is corroborated by clinical evidence of connectivity dysfunctions in sensorimotor \(97\) and frontostralial \(98\) networks observed
in patients with FASD. Additional data also indicate heightened coherence and hyperexcitability of piriform cortex-hippocampal networks on cue-presentation, which seems to rely on aberrant excitatory synapse facilitation (99,100). Moreover, mice with FAE display enhanced functional connectivity between OFC and striatum during specific phases of reversal learning (101). Importantly, while these preclinical results point to a generalized potentiation of corticostriatal circuits, contrasting evidence indicates that FAE decreases MSN excitability in posterior, but not anterior, DMS and reduces goal-directed behavior in male offspring only (102). These data highlight how defined corticostriatal pathway, subregional specialization, sex, alcohol exposure protocol, and behavioral task design play a role in the interpretation of the effects of FAE-induced circuit dysfunctions underlying specific behavioral deficits. Despite the need for pathway- and region-specific investigation of FAE-induced deficits, these data indicate that FAE affects corticostriatal development. Considering that appropriate synaptic transmission at different inputs underlies multiple executive function aspects, FAE-induced deficits at distinct corticostriatal pathways might contribute to cognitive dysfunctions.

**MODEL 1: ASSOCIATIVE-SENSORIMOTOR IMBALANCE**

A model of striatal action selection posits that a “go-circuit” engages an associative pathway (OFC-DMS) during goal-directed actions and sensorimotor (M1/S1-DLS) circuits during habitual behaviors (Figure 2) (58,103). Thus, rewards 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 pathway disrupt goal-directed behavior in favor of an overreliance on habitual responding, which is insensitive to outcome devaluation (104). Accordingly, activation of the OFC-DMS pathway promotes goal-directed behavior (105) while motor stereotypes rely on an increased functionality of motor areas (106). FAE-induced enhancement of operant responding depends on decreased function of parvalbumin-positive GABAergic interneurons (45), which leads to hyperexcitable MSNs in sensorimotor DLS (red square in Figure 2). However, while chemogenetic activation of parvalbumin-positive DLS GABAergic interneurons rescued the enhanced lever-pressing behavior, it did not restore habit formation in mice with FAE (45). This suggests that while enhanced lever pressing derives from dysfunctional sensorimotor loops, habit formation deficits might originate from associative corticostriatal impairments, whereby hyperactivation of the OFC-DMS pathway biases toward goal-directed strategies and destabilizes automatized patterns of responding (Figure 2). Importantly, this model works even if both pathways are hyperfunctional and 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 (107). In an animal model of obsessive-compulsive disorder (knock-out for Sapap3), abnormal automatized action repetition has been studied by developing a learning task of cue-induced self-grooming behavior (108). While cue-induced anticipatory grooming disappeared in wild-type mice, it was retained by Sapap3 KO mice and indicated a higher vulnerability to develop repetitive behaviors. This behavioral impairment was associated with stronger activation of striatal neurons. Importantly, enhancing feed-forward inhibition on MSNs via lateral OFC stimulation decreased compulsive grooming. Thus, these data further indicate that associative pathway activation prevents the expression of aberrantly automatized behavior.

As described above, EtOH exposure during brain development profoundly impacts behavioral flexibility, which also relies...
on the intact functionality of corticostratial associative pathways. In fact, neuronal impairments in both the OFC and DMS affect reversal learning in humans, primates, and rodents (11). While hypoactivation of the OFC characterizes deficits in reversal learning in animal models of obsessive-compulsive disorder (109), recent data suggest that synaptic strengthening and weakening of secondary motor cortex and OFC-striatal inputs, respectively, contribute to compulsive behavior in an obsessive-compulsive disorder model (110). Furthermore, the OFC-striatal associative pathway is hyperactive during specific phases of a reversal-learning task in FAE offspring (101). Thus, not only would hyperactive associative pathways impede habit formation, but the enhanced goal-directed behavior would also interfere with the formation of novel action-outcome associations, resulting in cognitive flexibility impairments (Figure 2).

**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 (10), requiring suppression of 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 SUDs (111) and FASD (44). Inactivation studies indicate that the IL and PL subdivisions of the mPFC suppress premature and nonspecific actions in instrumental tasks or inhibit behavioral responses in go/no-go tasks (112–116). Furthermore, while PL and IL projections to the dorsal striatum have been hypothesized to support goal-directed and habitual behavior, respectively, the IL projections to the ventral striatum (VS) seem to be involved in behavioral inhibition (117). Inactivation studies further indicate that the mPFC is necessary for appropriate reversal learning (118), most likely by suppressing obsolete action-outcome associations and/or actions dictated by previously learned sets of rules. This idea is corroborated by human imaging studies reporting impaired frontal (including prefrontal) striatal network activity during behavioral inhibition tasks in patients with FASD (119). These studies support a second model by which FAE-induced dysfunction of the infralimbic to VS pathway impairs behavioral inhibition and results in heightened operant responding and flexibility defects (Figure 3). Assessing resistance to punishment as a metric of perseverative and inflexible behavior would be interesting to probe the function of IL-striatal networks in mice with FAE. In fact, compulsive behavior seems to originate from hypofunctional mPFC-striatal circuits (120), which are normally recruited when an aversive stimulus is paired with cocaine administration to discontinue drug-taking.

This second model does not necessarily require functional impairments in associative or sensorimotor pathways, and striatal input from lateral PFC (or OFC) has also been implicated in behavioral response inhibition. In fact, depotentiation of OFC input reduced compulsive DA neuron self-stimulation in a model of reward-seeking despite punishment (121), and self-grooming is inhibited by OFC neuron stimulation via reduced MSN activity (108).

Recent data indicate that potentiation of mPFC inputs enhances operant responding in animal models of compulsivity. In fact, strengthening and depressing mPFC input to the dorsal striatum increases and decreases alcohol-seeking (122), respectively. These data indicate that potentiation of PL-striatal inputs might also participate in FAE-induced heightened operant responding. In fact, hyperengaged mPFC inputs, which are normally only recruited during the initial goal-directed phases of action learning (89), might enhance operant responding, impede habit formation, and counteract behavioral flexibility.

**MODEL 3: STRIATAL OUTPUT PATHWAY DEFICITS**

A third model of FAE-induced behavioral deficits involves disruption of striatal output pathway function (Figure 4). It has been proposed that discrete striatal neuron ensembles control action learning and execution (123). While early studies
proposed a go/no-go model with direct and indirect MSNs having opposing roles in behavioral execution (124,125), recent in vivo studies indicate that increased activity in both striatal output pathways is associated with hyperactivity (126) and action selection (127). To reconcile these 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 action execution (123). According to this idea, the FAE-induced increase in operant responding (45) might be mediated by exaggerated recruitment of direct MSNs within a given striatal ensemble (Figure 4). Direct MSN hyperactivity would largely prevail over the inhibitory function of indirect MSNs, resulting in aberrant action repetition. Moreover, the FAE-induced reversal learning deficits might reflect aberrant recruitment of novel striatal ensembles to update striatal output information and stabilize new behavioral patterns (Figure 4). The evidence that an endocannabinoid-mediated reduction in GABAergic tone enhances MSN excitability in DLS (45), possibly dysregulating striatal neuron ensemble function, further supports this idea. Finally, the role of dopamine in controlling both the recruitment of MSN ensembles (128) and the synaptic plasticity at lateral inhibitory synapses between MSNs (129,130) suggests that dysregulated dopamine signaling might also impair the local GABA-mediated control of striatal output function following FAE.

It is important to note that these models are not mutually exclusive (Figure 5). Deficits in cortical input most likely result in altered basal ganglia output. In fact, associative-sensorimotor input potentiation (PL- and OFC-DMS circuits over M1/S1-DLS, model 1) and/or decreased infralimbic-striatal (IL-VS) function (model 2) might dramatically affect the excitatory drive on MSNs. Imbalanced input function, dopamine deficits, and loss of local GABAergic control (model 3) might lead to MSN hyperrecruitment, resulting in heightened operant responding and reversal learning deficits (Figure 5). Thus, the characterization of abnormal corticostriatal circuits will allow for testing of the efficacy of preclinical interventions to ameliorate FAE-induced cognitive impairments.

**PRECLINICAL INTERVENTIONS FOR FETAL ALCOHOL EXPOSURE–INDUCED BEHAVIORAL DYSFUNCTIONS**

Despite very few clinical studies (131), there is a large body of preclinical literature focused on treatment of FAE-induced cognitive deficits (132). Although their mechanisms of action remain unclear, we discuss selected molecules that could potentially act on corticostral circuits to restore appropriate pathway function (Figure 5C). These interventions can be classified as protective (designed to prevent FAE symptoms), restorative (designed to attenuate neurobehavioral impairments when given during and after EtOH exposure), or acute (brief treatments to reduce symptoms in adolescents and adults). The polyphenol flavanoid dihydromyricetin protects against some FAE-induced behavioral dysfunctions (133). By
preventing alcohol-mediated enhancement of GABA<sub>A</sub> receptor function (133), dihydromyricetin counteracts E/I imbalance while preventing apoptosis and cortical degeneration. Similarly, when co-administered with EtOH at early postnatal stages, lithium prevents neurodegeneration, long-term potentiation deficits, and aberrant cortical paired-pulse facilitation via unknown molecular mechanisms (100). Lithium might restore plasticity deficits at cortical inputs to protect against FAE-induced behavioral inhibition impairments.

The phosphodiesterase type I inhibitor vinpocetine may have a restorative effect on corticostriatal plasticity in vivo. Vinpocetine restores ocular dominance plasticity in a ferret model of FAE (134). Considering the prominent role of phosphodiesterases in regulating intracellular cyclic AMP, a key second messenger modulated by dopamine and implicated in striatal synaptic plasticity (Figure 5C) (135), vinpocetine may restore the FAE-induced maladaptive corticostriatal plasticity. Choline supplementation during early postnatal days
ameliorsates deficits in both spatial learning and behavioral flexibility in FAE adolescent offspring (136). Choline is a precursor of the neurotransmitter acetylcholine. Among other functions, acetylcholine controls dopamine release via activation of muscarinic and nicotinic receptors (137). Importantly, acetycholine-mediated dopamine release is an important regulator of corticostriatal plasticity (138). Thus, an intriguing hypothesis is that choline promotes acetylcholine production, which in turn could modulate and normalize dopamine release, regulate dopamine-dependent plasticity, and restore corticostriatal circuit function (Figure 5C) in mice with FAE.

The neuroprotective peptides NAPVSIPQ and SALLRSIPA, which are brain permeable on intranasal or systemic injection (139), appear to provide acute protection against learning impairments (140) and cortical NMDA receptor subunit composition deficits (141) in FAE rodents. Thus, appropriate expression of NMDA receptor subunits might re-establish normal corticostriatal function (Figure 5C) and be beneficial in rescuing cognitive dysfunctions.

In recent years, several clinical trials successfully tested the ability of brain stimulation protocols to ameliorate behavioral symptoms of certain neuropsychiatric disorders (142). Among these, transcranial direct-current stimulation of dorsolateral PFC improved attention on continuous training to enhance cognitive function in children with FASD (143). Altogether, these data indicate the potential of corticostriatal preclinical interventions to ameliorate FASD symptoms.

CONCLUSIONS

The lack of knowledge about brain circuits related to FASD cognitive symptoms could be improved using ex vivo and in vivo recordings of synaptic and circuit function to identify precise dysfunctional aspects of corticostriatal circuits and tailor precise translational strategies. These experiments would have particularly high translational value because they can also target other FASD traits, such as socioemotional dysfunctions, and/or similar neurobehavioral symptoms of other neuropsychiatric disorders.

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