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The effects of early life stress on impulsivity

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Abstract

Elevated impulsivity is a symptom shared by various psychiatric disorders such as substance use disorder, bipolar disorder, and attention-deficit/hyperactivity disorder. However, impulsivity is not a unitary construct and impulsive behaviors fall into two subcategories: impulsive action and impulsive choice. Impulsive choice refers to the tendency to prefer immediate, small rewards over delayed, large rewards, whereas impulsive action involves difficulty inhibiting rash, premature, or mistimed behaviors. These behaviors are mediated by the mesocorticolimbic dopamine (DA) system, which consists of projections from the ventral tegmental area to the nucleus accumbens and prefrontal cortex. Early life stress (ELS) alters both impulsive choice and impulsive action in rodents. ELS also changes DA receptor expression, transmission, and activity within the mesocorticolimbic system. This review integrates the dopamine, impulsivity, and ELS literature to provide evidence that ELS alters impulsivity via inducing changes in the mesocorticolimbic DA system. Understanding how ELS affects brain circuits associated with impulsivity can help advance treatments aimed towards reducing impulsivity symptoms in a variety of psychiatric disorders.

Keywords

stress; cognition; nucleus accumbens; prefrontal cortex; sex differences

1. Introduction

Impulsivity is acting without forethought. In some cases, it pays to act impulsively. For instance, when one is in a dangerous situation, acting impulsively (e.g., landing the first punch in a fight) may improve chances of survival. Additionally, acting on impulse can stimulate creative moments and allow one to seize opportunities that they may have otherwise missed. Most of the time, acting impulsively is not considered pathological. However, when impulsivity impacts everyday life, it can constitute a risk factor for a large number of life-threatening behaviors (Bari & Robbins, 2013; Everitt et al., 2008;

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Fineberg et al., 2014; Gut-Fayand et al., 2001). High impulsivity is associated with several psychiatric disorders including, attention-hyperactivity disorder (ADHD), bipolar disorder, and addiction (e.g., gambling disorder and substance use disorder, SUD) (Adler et al., 2017; Dawe & Loxton, 2004; Najt et al., 2007; Vest, Reynolds, & Tragesser, 2016).

Another factor associated with ADHD, bipolar disorder, and addiction is exposure to early life stress (ELS) (Halevi, Djalovski, Vengrober, & Feldman, 2016; Herzberg et al., 2018; Syed & Nemeroff, 2017). For instance, among adolescents receiving treatment for SUD, more than 70% report a history of trauma (Deykin & Buka, 1997; Funk, McDermeit, Godley, & Adams, 2003). Childhood trauma also predicts ADHD onset and is a risk factor for the persistence of ADHD symptoms into adulthood (Biederman et al., 1995; Sugaya et al., 2012; Vrijsen et al., 2018). Additionally, self-reported childhood abuse may be evident in about 50% of individuals with bipolar disorder and contribute to worse clinical outcomes (Farias et al., 2019; Garno, Goldberg, Ramirez, & Ritzler, 2005; Xie et al., 2018).

Much work has focused on how ELS impairs executive functioning, memory, and reward processing to understand mechanisms by which ELS may increase risk for psychiatric disorders (Hostinar, Stellern, Schaefer, Carlson, & Gunnar, 2012; Pechtel & Pizzagalli, 2011). However, fewer studies have focused on how ELS affects impulsivity, even though impulsivity is a feature of ADHD, bipolar disorder, and SUD. This review brings together data on what is known about ELS and impulsivity. We first describe types of impulsive behaviors and the circuits that underly impulsive processes. Then, we detail how ELS affects impulsivity and the purported mechanisms by which this can occur. Throughout preclinical to clinical findings are compared, and when known, sex differences in these effects are detailed. Given the number of disorders with ELS as a risk factor and impulsivity as a key feature, understanding the mechanisms by which early stress affects impulsivity may lead to novel treatments that improve outcomes for a variety of conditions.

2. Different Types of Impulsive Behaviors

Because impulsivity is a multifaceted construct, an attempt to categorize impulsivity has been to organize impulsive behaviors into three distinct types (Robbins & Dalley, 2017). The first type, waiting impulsivity, encompasses impulsive behaviors that require a subject to wait before getting a reward. Behaviors associated with this branch are measured using delay discounting, differential-reinforcement-of-low-rates-of-responding (DRL), and five-choice-serial-reaction-time tasks (5-CSRTT). For DRL and 5-CSRTT, impulsivity depends on the ability to prevent an inappropriate, premature response. Inability to withhold a premature response is termed an impulsive action. In delay discounting, impulsivity is associated with choosing a small, immediate reward over a large, delayed one. A subject's preference for instant gratification over delayed gratification is considered an impulsive choice. The second branch, risky impulsivity, refers to a subject's preference for uncertain but bigger outcomes. A task used to measure this type of behavior in rodents is the probability discounting task, which involves choosing between two levers: one dispenses a small reward every time it is pressed versus another which dispenses a larger reward sometimes (risky lever). Choosing the riskier option is indicative of higher levels of impulsivity and these responses can be considered a form of impulsive choice. However, there is some debate as to whether risky

behavior is the same as impulsivity. For example, studies that use delay and probability discounting show that steeper discounting in one measure does not predict the results of the other, suggesting these processes are actually different (Herman, Critchley, & Duka, 2018; Holt, Green, & Myerson, 2003). Nevertheless, risk-taking is closely related to impulsivity and can predict the likelihood of one pursuing hazardous behavior (Donohew et al., 2000). Finally, the last type, stopping impulsivity, refers to the inability to stop a response after it has been initiated. Tasks commonly used to measure stopping behavior are go-no-go and stop-signal reaction time task. Given these tasks require stopping an initiated action, they also measure impulsive actions.

Differentiating between various forms of impulsivity not only has implications for experimental design but also for understanding risk factors for psychiatric disorders. There is evidence that different forms of impulsivity are associated with disorders to varying degrees. For example, some evidence suggests pathological gambling is associated with impulsive action but not impulsive choice (Brevers et al., 2012). In ADHD, both impulsive choice and impulsive action are disrupted but these measures relate to different symptoms: increased impulsive choice is associated with a broad range of ADHD symptoms, including hyperactivity, while impulsive action is related more specifically to executive control (Solanto et al., 2001). Parsing impulsivity is also informative for understanding different aspects of SUD (Broos et al., 2012). In a rodent model of nicotine seeking, impulsive action was associated with an enhanced motivation for nicotine self-administration, while impulsive choice was associated with enhanced vulnerability to cue-induced relapse (Diergaarde et al., 2008). These distinctions are driven by the differences in circuitry, which will be detailed below. Collectively, these data underscore the value of studying distinct aspects of impulsivity.

3. Dopamine Modulates Impulsivity

Dopamine (DA) is linked to impulsivity in humans and rodents. Clinically, disorders with high impulsivity as a key feature are commonly associated with DA dysregulation (Ashok et al., 2017; Pettorruso et al., 2019; Rosa-Neto et al., 2005; Whitton, Treadway, & Pizzagalli, 2015). It is believed that hypodopaminergic function may contribute to drug abuse and underlie behavioral abnormalities observed in ADHD and bipolar disorder (Badgaiyan, Sinha, Sajjad, & Wack, 2015; Berk et al., 2007; Blum et al., 2008; D. A. Cousins, Butts, & Young, 2009; Fattore & Diana, 2016; Gold, Blum, Oscar-Berman, & Braverman, 2014; Sanna, Fattore, Badas, Corona, & Diana, 2021). Administration of psychostimulants, like amphetamine or methamphetamine, are often prescribed for ADHD or bipolar disorder to help reduce impulsivity symptoms (Perugi, Vannucchi, Bedani, & Favaretto, 2017; Wolraich et al., 2019). These types of drugs block DA transporters (DAT), which promotes increased DA levels in the brain (Kuczenski & Segal, 1997). Although these treatments can help alleviate impulsive symptoms in these disorders, nonmedical use of stimulants by people who do not have these disorders promotes impulsive behaviors (Grant, Redden, Lust, & Chamberlain, 2018; Messina et al., 2014).

By using rodent models, we can more specifically parse how changes in DA signaling impact different types of impulsive behavior. Acute administration of amphetamine

(0.25–1mg/kg) in rodents often increases premature responses and impairs behavioral inhibition (Baarendse & Vanderschuren, 2012; Britton & Koob, 1989; Caballero-Puntiverio, Fitzpatrick, Woldbye, & Andreasen, 2017; Hayton, Maracle, & Olmstead, 2012; van Gaalen, Brueggeman, Bronius, Schoffelmeer, & Vanderschuren, 2006). However, acute doses of this same drug can also reduce premature responding (Hayton et al., 2012). For instance, rats trained on a response inhibition task, which requires them to withhold pressing a lever until signaled to do so, amphetamine administration increases their impulsive action when the delay to respond is fixed, but reduces it when the delay is variable (Hayton et al., 2012). Therefore, acute doses of amphetamine can alter impulsive action and its effect may depend on the subject's expectation of task demands. Chronic administration (5mg/kg/day) of other DA agonist drugs, like ropinirole hydrochloride, can also increase premature responding, especially when the cues to the reward are signaled (Tremblay, Barrus, Cocker, Baunez, & Winstanley, 2019). Cues predicting reward elicit activity in dopaminergic neurons, which has been shown to sensitize rats to the hyperlocomotor effects of stimulants (Zack, Featherstone, Mathewson, & Fletcher, 2014).

Interestingly, acute, low doses of stimulant administration can improve the ability to wait for large rewards (S. B. Floresco, M. T. Tse, & S. Ghods-Sharifi, 2008; Wade, de Wit, & Richards, 2000; Catharine A. Winstanley, Dalley, Theobald, & Robbins, 2003). For instance, low doses of amphetamine (0.01–0.25 mg/kg) can shift choice towards large, delayed rewards on delay discounting tasks, therefore reducing impulsive choice (S. B. Floresco et al., 2008; van Gaalen, van Koten, Schoffelmeer, & Vanderschuren, 2006). Similarly, DAT blockade, which also results in an increase in DA levels, reduces impulsive choice (van Gaalen, van Koten, et al., 2006). However, some studies have reported that elevations in DA do not always decrease or affect impulsive choice (Cardinal, Robbins, & Everitt, 2000; Evenden & Ryan, 1996; Helms, Reeves, & Mitchell, 2006; Zeeb, Soko, Ji, & Fletcher, 2016). In one study, high doses of amphetamine (1–3mg/kg) decreased lever pressing and chow consumption in a lever pressing/feeding choice procedure (M. S. Cousins, Wei, & Salamone, 1994). Therefore, lower doses, but not higher levels of psychostimulants, increase choice for larger, delayed rewards.

Even though it is tempting to assume increases in DA levels decrease impulsive choice and increase impulsive action, it is possible the effects of DA on impulsivity are less linear and instead an inverted-U relationship. In other words, depending on where one lands on the curve, shifts in DA levels, can improve or impair impulsivity symptoms (J. W. Dalley & Roiser, 2012). For instance, oral administration of methylphenidate reduces impulsivity only in high, but not low, impulsive rats as determined by the 5-CSRTT (Caprioli et al., 2015). These results suggest that the efficacy of certain stimulant treatments is baseline-dependent and is comparable to the efficacy of psychostimulants in human populations. For instance, treatments that can benefit impulsive individuals (presumably with suboptimal baseline DA signaling) can also impair performance in people who have low levels of impulsivity (de Wit, Crean, & Richards, 2000; Petzold et al., 2019).

Genetic factors can also influence the effect of DA on impulsive behavior (J. W. Dalley & Roiser, 2012; Loos et al., 2010; Simon et al., 2013). For instance, lower dopamine 2 (D2) mRNA receptor expression in the nucleus accumbens (NAc) is correlated with

higher impulsive action (Simon et al., 2013). These results are similar to positron emission tomography or autoradiography studies that show impulsive rats have reduced D2 receptor availability in the NAc (Dalley et al., 2007; Jupp et al., 2013). Similar reductions in ventral striatal D2 receptors are also found in highly impulsive methamphetamine-dependent individuals (Kohno et al., 2016; Lee et al., 2009; London, 2020). These findings suggest the expression of DA-related genes influence impulsive traits. Collectively, these studies highlight DA's involvement in impulsivity.

One caveat with these data is that they were collected only in male rodents. However, many studies have highlighted the fact that there are sex-specific effects in DA circuitry that are influenced by gonadal, chromosomal, and epigenetic factors (reviewed in, (Jill B. Becker & Chartoff, 2019; Eck & Bangasser, 2020; Kokane & Perrotti, 2020; Zachry et al., 2021). For instance, males, but not females, overproduce D1 and D2 receptors in the striatum early in development (25–40 days, the onset of puberty) (Susan L. Andersen, Rutstein, Benzo, Hostetter, & Teicher, 1997; S. L. Andersen & Teicher, 2000). In adulthood, circulating levels of ovarian hormones can alter DA (J. B. Becker, 1990). Baseline firing activity of DA neurons in the VTA of male and female rodents is similar (Locklear, Michaelos, Collins, & Kritzer, 2017; Rincón-Cortés & Grace, 2017), however, electrically stimulated phasic DA release in the VTA is higher in estrus females as compared to males or non-estrus females (Calipari et al., 2017). These data illustrate that there are sex differences in the DA system and highlight the importance of including both sexes in experimental designs.

It is clear that DA has a key role in regulating impulsivity. This review will focus on the role of DA and the mesocorticolimbic system because these endpoints have been more thoroughly investigated in ELS studies relevant to impulsivity than other endpoints. However, the neurochemical basis of impulsivity is complicated and involves other neurotransmitter systems, including serotonin (5-HT) and norepinephrine (NE) (J. W. Dalley, Mar, Economidou, & Robbins, 2008; J. W. Dalley & Roiser, 2012; Groman, 2020; Johansson, Bergvall, & Hansen, 1999; Piña et al., 2020; Swann et al., 2013; Zaniewska, Filip, & Przegalinski, 2015). For example, reducing 5-HT levels increases impulsive action in humans and rodents (Harrison, Everitt, & Robbins, 1997; Worbe, Savulich, Voon, Fernandez-Egea, & Robbins, 2014). NE also impacts impulsive action. Administration of selective NE reuptake inhibitor, atomoxetine, significantly decreases premature responding on a 5-CSRTT (Economidou, Theobald, Robbins, Everitt, & Dalley, 2012). Regulating NE also affects impulsive choice. For example, blocking NE transporter function and activating α2 adrenergic receptors decreases impulsive choice (S. Kim, Bobeica, Gamo, Arnsten, & Lee, 2012; Nishitomi et al., 2018; Robinson et al., 2008). These studies highlight the complexity of neural mechanisms underlying impulsivity. More research, particularly in how ELS-induced alterations in 5HT and NE mediate impulsivity, is needed.

3.1 The NAc and Impulsivity—The NAc is a major component to the ventral striatum that receives DA and facilitates reward-seeking (Berridge & Robinson, 1998; Salamone, 1994; Trifilieff et al., 2013). The NAc is commonly subdivided into two parts: the core and shell (Zahm & Brog, 1992). Inputs from cortical and striatal brain areas display unique topographical organization throughout the NAc (Brog, Salyapongse, Deutch, & Zahm, 1993; H. J. Groenewegen, der Zee, te Kortschot, & Witter, 1987; Kelley & Domesick,

1982; Spooren, Veening, Groenewegen, & Cools, 1991). Dorsal structures like the anterior cingulate cortex (ACC), target the NAc core, while ventral structures like the basolateral amygdala (BLA) and infralimbic cortex target the NAc shell (Brog et al., 1993; H. J. Groenewegen, Wright, Beijer, & Voorn, 1999; Sesack, Deutch, Roth, & Bunney, 1989). Some structures, such as the orbitofrontal cortex (OFC), project to both the core and shell (Brog et al., 1993). Efferent fibers of the NAc as a whole project to the midbrain, hypothalamus, and ventral pallidum as well as other motor systems (Brog et al., 1993; Henk J. Groenewegen & Russchen, 1984). As such, the NAc is a hub that receives and relays information to motor association sites in charge of carrying out appropriate behaviors.

NAc functions are regulated by DA. DA signaling in the NAc can occur via two classes of DA receptors. D1-like receptors (D1 and D5 receptors) stimulate postsynaptic adenylyl cyclase activity and causes increased neuronal firing, while D2-like receptors (D2, D3, and D4 receptors) inhibit this signaling which causes a reduction in firing (Gingrich & Caron, 1993; Hopf, Cascini, Gordon, Diamond, & Bonci, 2003; Sibley & Monsma, 1992; Surmeier, Ding, Day, Wang, & Shen, 2007). Medium spiny neurons (MSNs) in the NAc can also express either D1 or D2 receptors, which can exert opposing control over NAc functions (Bariselli, Fobbs, Creed, & Kravitz, 2019; Gerfen, 1992; Lobo & Nestler, 2011).

Work from van Gaalen has highlighted the involvement of D1 and D2 receptors in regulating impulsive action and impulsive choice. For instance, systemic blockade of D1 receptors increases impulsive choice (van Gaalen, van Koten, et al., 2006). Antagonizing D2 receptors has no effect on behavior on its own, but when followed by systemic amphetamine administration, it can block premature responding and impulsive choice (T. Pattij, Janssen, Vanderschuren, Schoffelmeer, & van Gaalen, 2007; van Gaalen, van Koten, et al., 2006). These data suggest that DA D1 and D2 receptors play important, but perhaps distinct roles, in impulse control. However, recent work finds D1 and D2 neurons express similar activity profiles during periods of behavioral suppression (Lafferty, Yang, Mendoza, & Britt, 2020). Therefore, rather than working in opposition, D1 and D2 expressing neurons may exhibit complementary activity in the NAc to regulate behavioral outcomes.

Impulsive action is modulated by DA signaling in the NAc. For instance, selectively antagonizing D1 receptors in the NAc reduces impulsive action (T. Pattij et al., 2007). In contrast, low NAc D2 receptor expression, which reduces DA inhibitory drive, is associated with increased premature responding in rats (Jupp et al., 2013). Therefore, increasing DA signaling in the NAc may elevate impulsive action. After all, increasing DA signaling by reducing DAT function in the NAc increases impulsive action (Jupp et al., 2013). Interestingly, these effects are specific to the NAc shell and high DA release to the shell is associated with increased premature responding (Diergaarde et al., 2008). Moreover, lesions to the NAc shell block amphetamine-induced premature responding, which may disrupt DA related effects of this stimulant (E. R. Murphy, Robinson, Theobald, Dalley, & Robbins, 2008). These findings have led to the idea that premature responding is due to excess DA levels in the shell region of the NAc (J. W. Dalley & Robbins, 2017).

While increased dopaminergic drive in the NAc shell increases impulsive action, evidence suggests that decreased dopaminergic drive in the NAc core increases impulsive choice.

Specifically, overexpression of DAT in the NAc core, which would lower levels of available DA, increases impulsive choice (Adriani et al., 2009). Additionally, D1 antagonism in the NAc core decreases sensitivity to reinforcer magnitudes (Justin R. Yates & Bardo, 2017). In other words, blocking D1 signaling shifts preference away from large rewards even when its delivery is immediate. A potentially contrary finding is that reduced D2/3 receptor binding in the NAc core is associated with impulsive choice (Barlow et al., 2018). A reduction in postsynaptic D2/3 receptors would increase dopaminergic tone in the NAc. However, presynaptic D2 receptors on dopaminergic neurons act as autoreceptors, limiting DA synthesis and release (Beaulieu & Gainetdinov, 2011; Gingrich & Caron, 1993). Viral knockdown of D2 presynaptic receptors in the VTA, the major source of dopamine for the NAc, increases choice impulsivity (Bernosky-Smith et al., 2018). Taken together, these studies support the idea that reducing dopaminergic drive in the NAc core increases impulsive choice.

Electrophysiology studies also support pharmacological data that DA signaling in the NAc regulates impulsivity (Pan, Schmidt, Wickens, & Hyland, 2005; M. R. Roesch, Calu, & Schoenbaum, 2007; Saddoris, Sugam, et al., 2015). Phasic DA release in the NAc tracks certain aspects of value-based decision-making (M. R. Roesch et al., 2007; Saddoris, Sugam, et al., 2015). This is interesting because phasic DA bursts are known to occur in response to reward-predictive cues (Day, Jones, Wightman, & Carelli, 2010; Schultz, Dayan, & Montague, 1997), whereas dips in DA firing are associated with omissions of expected reward (Saddoris, Sugam, et al., 2015). One study that only used female rats found that bursts and dips in phasic DA signaling could function as a teaching signal to facilitate reward-related learning (Steinberg et al., 2013). Indeed, studies that override or inhibit phasic DA signals have shown that this can change behavior in male rodents (Fitzpatrick et al., 2019; Stopper, Tse, Montes, Wiedman, & Floresco, 2014). For instance, suppressing DA bursting that typically occurs when a rat chooses its preferred reward option will biases it to discontinue selecting that option in subsequent trials (Saddoris, Sugam, et al., 2015). Lastly, each subregion of the NAc encodes DA signaling differently: DA release to core is associated with tracking value of predicted outcomes, whereas DA release to shell tracks motivationally salient stimuli (Saddoris, Cacciapaglia, Wightman, & Carelli, 2015). These data indicate that neurons in the NAc core and shell can encode DA signaling differently and further supports the notion that each subregion has dissociable effects in regulating impulsivity.

It is unclear why the NAc core and shell may have dissociable roles in impulsive control. However, dissociations between the core and shell are reported for a number of behaviors such as inhibitory avoidance (Piantadosi, Yeates, & Floresco, 2018), effort-based decision making (Ghods-Sharifi & Floresco, 2010), cue-induced reinstatement of food-seeking behavior (Floresco, McLaughlin, & Haluk, 2008), motivational conflict (Piantadosi, Yeates, Wilkins, & Floresco, 2017), and incentive-cue responding (Ambroggi, Ghazizadeh, Nicola, & Fields, 2011). Data from these studies suggest that the shell inhibits inappropriate actions, while the core promotes approach behaviors towards stimuli that likely yield rewards. Future studies should continue to investigate the differences between these two NAc subregions. These studies could provide insight into the mechanisms that may underlie disorders that are characterized by difficulties in restraining maladaptive behavior, impulsivity, and abnormal

activity in the NAc (Engeli et al., 2021; Hoogman et al., 2013; Ma et al., 2016; Stark et al., 2011). A schematic depicting the role of the NAc core and shell in impulsive action and impulsive choice is shown in Figure 1. Notably only one of the above studies used females instead of males and none compared the sexes, so more studies including both sexes are needed to identify any similarities/differences in DA signaling in the NAc.

4. Cortical Involvement in Impulsivity

In addition to the NAc, different areas of the prefrontal cortex are associated with mediating different forms of impulsivity. In particular, the OFC and medial prefrontal cortex (mPFC) play important roles in impulsivity (Dalley & Ersche, 2019; Dalley, Everitt, & Robbins, 2011).

The OFC can mediate impulsive choice in rodents and humans (Bechara, Tranel, & Damasio, 2000; Mar, Walker, Theobald, Eagle, & Robbins, 2011; Mobini et al., 2002; Tommy Pattij & Vanderschuren, 2008; Zeeb, Floresco, & Winstanley, 2010). Several studies have reported changes in impulsive behavior in OFC-lesioned rats. Some studies report OFC lesions make male and female rats more impulsive and less likely to wait for delayed rewards (Mobini et al., 2002; Rudebeck, Walton, Smyth, Bannerman, & Rushworth, 2006). These results suggest that the OFC is necessary for responding when rewards are delayed. Others report that OFC lesions make rats less impulsive, which may indicate it is necessary for devaluing the delayed reward (C. A. Winstanley, Theobald, Cardinal, & Robbins, 2004). Possible reasons for the discrepancies are attributed to the heterogeneity of the OFC region, as well as when the lesion took place (e.g., pre-training vs. post-training). For example, when OFC lesions occur prior to the training on a gambling task, rats take longer to reach task acquisition (Zeeb & Winstanley, 2011). OFC lesions that occur after training, however, have no effect on risky choices on this task. These findings point to the OFC being involved in learning and that lesions that occur early in training could cause impairments in tracking outcomes to guide future responding. Single unit electrophysiological recordings also illustrate a role for the OFC in delay discounting behavior. Activity of different neurons in the OFC reflected a rat's preference for immediate, small rewards or large, delayed rewards (Roesch, Taylor, & Schoenbaum, 2006). These results suggest that different groups of neurons in the OFC track delayed rewards and outcome expectancies. Additionally, attenuating neural activity in the OFC, while simultaneously enhancing NAc neural activity, impairs impulse control (Meyer & Bucci, 2016). Collectively, these data provide evidence that the OFC modulates impulsive choice behavior.

The OFC mediates impulsive action behaviors associated with stopping impulsivity—the inability to stop an already initiated response. Lesions to the OFC reduce the ability of male rats to stop an inappropriate response on stop-signal tasks (Eagle et al., 2008). Additionally, decreased OFC DAT function is associated with high impulsive action on go/no-go tasks, suggesting hyperdopaminergic tone in the OFC mediates increased impulsive action (J. R. Yates, Darna, Beckmann, Dwoskin, & Bardo, 2016). Neural activity in the OFC is also associated with two distinct stopping mechanisms: proactive and reactive stopping (Balasubramani, Pesce, & Hayden, 2020; Hardung et al., 2017). Reactive stopping refers to situations in which subjects are required to stop in response to an external cue, whereas

proactive stopping develops according to the subjects internal goals (Aron, 2011). Despite its involvement in stopping impulsivity, the OFC does not appear to mediate impulsive action behaviors associated with waiting impulsivity. For instance, lesions to the whole OFC do not promote impulsive action behaviors on the 5-CSRTT in male rats (females were not tested) (Chudasama et al., 2003), however more data is needed.

Another cortical region involved in impulse control is the mPFC. The mPFC is associated with impulsive action as it plays a role in restraining premature responses (Cho & Jeantet, 2010; B. Li, Nguyen, Ma, & Dan, 2020; Tommy Pattij & Vanderschuren, 2008). For example, optogenetic inhibition of the mPFC in male rats affects proactive motor control (Hardung et al., 2017). Additionally, projections from the dorsomedial PFC to the subthalamic nucleus (STN) can inhibit premature responding (B. Li et al., 2020). The STN is a structure implicated in motor control and STN lesions can increase impulsive action (Baunez, Nieoullon, & Amalric, 1995; Guillaumin, Serra, Georges, & Wallén-Mackenzie, 2021; Uslaner & Robinson, 2006). These results suggest that the mPFC can signal to downstream structures like the STN to suppress inappropriate motor driven responses. Functional disconnection of the mPFC-NAc pathway also increases impulsive actions, an effect attributed to disrupting this “top-down” control over behavior (Christakou, Robbins, & Everitt, 2004). One caveat with mPFC lesion studies is that sometimes they may include the ACC (Cho & Jeantet, 2010; Pezze, Dalley, & Robbins, 2009). The ACC itself is involved in many different processes related to impulsivity such as error detection, cognitive control, and response selection (Bryden, Johnson, Tobia, Kashtelyan, & Roesch, 2011; Bussey, Everitt, & Robbins, 1997; Newman, Creer, & McGaughy, 2015). It is thought that the ACC is involved in detecting situations where behavioral response is ineffective and processes this information to guide behavior. Lesions to the ACC increases premature responses and reduces accuracy on the 5-CSRTT (Chudasama et al., 2003; Muir, Everitt, & Robbins, 1996). Additionally, activation of layer-5 pyramidal cells of the ACC impairs behavioral disinhibition (van der Veen et al., 2021). Thus, both the mPFC and ACC modulate impulsive action.

Neurons in the mPFC are also engaged during impulsive choice. Using electrophysiological recordings during a delay discounting task in male and female rats, Sackett and colleagues found that neurons in the prelimbic region of the mPFC respond to either large/delay options, small/immediate option, or both options (Sackett, Moschak, & Carelli, 2019). As the delays increased, so did the percentage of neurons that responded to small/immediate options. A rat’s baseline levels of impulsivity also influenced neuronal recruitment: highly impulsive rats demonstrated a greater percentage of small/immediate-responsive neurons as the task progressed than low impulsive rats. These results suggest that some neurons in the prelimbic cortex encode reward value.

Like the NAc, these cortical regions receive dopaminergic input from the VTA (Oades & Halliday, 1987). DA in the cortex can also modulate impulsivity (Puumala & Sirviö, 1998). Dopaminergic depletion in the OFC of rats decreases impulsive choice (Kheramin et al., 2004). This finding may indicate high levels of DA in the OFC may underlie discounting behavior. *In vivo* microdialysis data support this idea by finding increased levels of 3,4-dihydroxyphenylacetic acid (DOPAC) when rats make delay discounting judgements

(C. A. Winstanley, Theobald, Dalley, Cardinal, & Robbins, 2006). Increases in DOPAC could reflect increased DA utilization occurring in the OFC during delay discounting. Additionally, intra-OFC administration of a D1 receptor antagonist, SCH23390, decreases impulsive action in highly impulsive male rats (C. A. Winstanley et al., 2010). This result is similar to work showing systemic administration of D1 antagonists reduces impulsive behavior (van Gaalen, Brueggeman, et al., 2006; van Gaalen, van Koten, et al., 2006). In regards to the mPFC, antagonism of D1 and D2 receptors reverses the effects of amphetamine-induced premature actions and improves timing of responses (Cheng & Liao, 2017). However, low D2 mRNA receptor expression in the prelimbic region of the mPFC is correlated with high impulsivity (Simon et al., 2013). Additionally, male rats that are pretreated with either D1 or D2 receptor antagonists prior to delay discounting have higher levels of impulsive choice (Pardey, Kumar, Goodchild, & Cornish, 2012). Altogether, these data indicate that DA in the OFC and mPFC can also affect impulsivity.

5. ELS and Impulsivity

5.1 Models of Early Life Stress—

ELS in rodents can be studied using a variety of different models which include prenatal stress, as well as postnatal stress. These models have helped researchers further understand stress effects on impulsive behavior. Models of prenatal stress aim to stress a pregnant dam during different time-points of gestation (e.g., early, middle, or late) by using various stressors (e.g., restraint, noises, and lights), and different lengths of time (e.g., 3 times a day vs. 3 weeks) (Mueller & Bale, 2008; Soares-Cunha et al., 2018; Van den Hove et al., 2006; Weston, Weston, Allen, & Cory-Slechta, 2014; Wilson, Schade, & Terry, 2012). Offspring of stressed pregnant dams typically exhibit elevated corticosterone release in response to an acute stress exposure (30 min of restraint), which indicates heightened hypothalamic-pituitary-adrenal (HPA) axis reactivity (Cory-Slechta, Virgolini, Thiruchelvam, Weston, & Bauter, 2004; Soares-Cunha et al., 2018).

Postnatal models of stress in rodents typically involve some form of scarcity, where resources are removed. Maternal separation models are used as a postnatal stressor, and they disrupt dam-pup interactions by separating the pups from their mother for intermittent periods (e.g., 15 minutes to 24 hours per day) for one to three weeks postnatally (Millstein & Holmes, 2007; Molet, Maras, Avishai-Eliner, & Baram, 2014). Shorter variations of this model are increase levels of maternal care and stress resiliency in offspring; however, longer variations induce impaired maternal care (Eck & Bangasser, 2020; Nishi, Horii-Hayashi, & Sasagawa, 2014). To control for variations in maternal care, some manipulations employ artificial rearing procedures, where pups are separated from dams and experimenters mimic various amounts of pup care (e.g., low or high) with “maternal licking-like stimulations” via a wet paintbrush (Burton et al., 2007; Lovic, Keen, Fletcher, & Fleming, 2011). Another postnatal stressor is the limited bedding and nesting (LBN) manipulation, which is typically implemented during a pup’s first week of life (postnatal day 2–9). This low resource environment aims to mimic aspects of poverty (Eck et al., 2019; Gilles, Schultz, & Baram, 1996; Molet et al., 2014). This manipulation induces stress in dams, altering their maternal care towards their developing pups (Ivy, Brunson, Sandman, & Baram, 2008; Rice, Sandman, Lenjavi, & Baram, 2008). One of the advantages of the LBN paradigm

compared to other models is that it can induce changes in maternal care with limited external experimenter interventions. Rather than physically removing the dam from her pups to induce changes in maternal care, the LBN manipulation causes changes in care by altering the environment the animals are placed in. Additionally, data from human studies of chronic childhood stress, including war, poverty, and neglect/abuse suggest that the mother is typically present, even though her behavior may be abnormal (Halevi et al., 2016; Mulder, Kuiper, van der Put, Stams, & Assink, 2018; Wang, Choi, & Shin, 2020). Thus, this model is thought to have strong translational potential (Walker et al., 2017).

Even though stress from ELS models can dissipate quickly, exposure to these stressful manipulations early in life can cause long-lasting changes to reward-related networks (Dubé et al., 2015; Eck et al., 2019; Huang, 2014). Utilization of these models has also allowed researchers to better understand the neurobiological mechanisms underlying how stress persistently alters behavior. The type/severity of stress experienced, as well as the timing and duration of the stressor can influence its specific outcomes on the brain and behavior. Although different models of ELS may produce slightly different results, they have been useful for examining mechanisms that induce or ameliorate impulsive behavior.

5.2 Dissociable Effects of Early Life Stress on Impulsivity—Relatively few studies have examined how prenatal stressors affect impulsive action. One study did find that male and female rats exposed to prenatal stress made more premature responses on a challenging version of the 5-CSRTT (Wilson et al., 2012). Specifically, when the intertrial interval times increased, these rats were unable to withhold responding as compared to controls. In regard to postnatal stressors, work from Lovic and colleagues found that male and female rats that undergo a severe form of early life deprivation—artificial rearing with low simulated grooming—are unable to withhold premature responses as adults compared to control rats while performing DRL tasks (Lovic et al., 2011). Similarly, male rats which experienced maternal deprivation, make significantly more premature responses while performing the 5-CSRTT as compared to controls (Kentrop et al., 2016). Females however were not examined in this study. Together, these studies indicate that ELS can increase impulsive action. Table 1 summarizes the effects of ELS on impulsivity.

In contrast to the enhancing effect of ELS on impulsive action, ELS tends to decrease impulsive choice. Prenatal stress and exposure to low levels of lead reduces impulsive choice in males but has no effects in females (Weston et al., 2014). Similarly, maternal separation plus early social isolation reduces impulsive choice on delay discounting tasks in male but not female rats (Lovic et al., 2011). Reductions in impulsivity in delay discounting also have been found in male, but not female rats that were reared in LBN (Ordoñes Sanchez et al., 2021). In contrast, female, but not male rats, exposed to a surrogate mother while simultaneously being raised in a low resource environment early in life had reduced impulsivity in delayed discounting (Fuentes et al., 2014). These discrepancies between these studies in the sex impacted suggest that the social experience of having a surrogate mother may affect the sexes differently. One study found that ELS increases impulsive choice (Gondré-Lewis et al., 2016) but this finding is complicated by the fact that offspring were trained on operant binge drinking paradigms prior to learning delay discounting. Taken

together the literature suggest that ELS typically decreases impulsive choice (Table 1). However, much more work, particularly with prenatal models, is needed.

It is important to mention that some studies report that ELS can induce compulsive-like, rather than impulsive-like, behaviors (Boutros, Der-Avakian, Markou, & Semenova, 2017; Fuentes et al., 2014). Compulsive behaviors are repetitive, often purposeless, and lead to unfavorable outcomes. For instance, male offspring that experienced maternal separation showed increased perseverative responding (i.e., continued nose-poking after a correct response) on a 5-CSRTT task (Boutros et al., 2017). However, this experiment also included rats that were exposed to ethanol during adolescence (PND28–57), which could affect the interpretation of these results. Future studies should continue examining whether other prenatal and postnatal stressors also induce similar findings. Overall, the rodent literature demonstrates that ELS can lead to increases in impulsive action but decreases in impulsive choice.

6. Effects of ELS on the Mesocorticolimbic System Can Mediate Impulsivity

As mentioned previously, there is a complex relationship between DA levels and impulsivity. Stimulants, which increase DA, increase impulsive action but decrease impulsive choice (Baarendse & Vanderschuren, 2012; Britton & Koob, 1989; Caballero-Puntiverio et al., 2017; S. B. Floresco, M. T. L. Tse, & S. Ghods-Sharifi, 2008; Hayton et al., 2012; van Gaalen, Brueggeman, et al., 2006; Wade et al., 2000). ELS can affect the mesolimbic DA system to increase dopaminergic drive (Baier, Katunar, Adrover, Pallarés, & Antonelli, 2012; Eck & Bangasser, 2020). For example, maternal separation increases the excitability of VTA DA neurons in female rats (males were not tested) (Spyrka et al., 2020). Maternal separation can also affect tyrosine hydroxylase (TH), the rate limiting enzyme of catecholamine synthesis. Specifically, maternal separation increases TH-immunoreactive cells in the VTA in adolescent male and adult female rats (Chocyk et al., 2011; Kapor et al., 2020). In the PFC and NAc, TH-immunoreactive fibers are denser following maternal separation in adolescent females (males were not tested) (Majcher-Maślanka, Solarz, Wędzony, & Chocyk, 2017). In studies that only tested male rats, prenatal stress increases DA transcription factors in the VTA and dopamine release in the NAc shell (the core was not analyzed) (Katunar, Saez, Brusco, & Antonelli, 2009; Silvagni et al., 2008). Although most of these studies do not directly compare males to females, the overall pattern is that ELS increases dopaminergic drive from VTA across sex.

In addition to increasing DA levels in the NAc, ELS can also alter DA receptor expression. Female, but not male, mice who experienced maternal separation plus social isolation show reductions in D1 receptor expression in the NAc (Sasagawa et al., 2017). A decrease in this receptor's expression in the NAc could reduce dopaminergic signaling in females and may help compensate the stress-induced increases in DA drive from the VTA. Changes in D1 expression are attributed to hypermethylation of the *Drd1a* promoter region, revealing an epigenetic modification that can explain this effect in females (Sasagawa et al., 2017). In contrast, exposure to a limited resource environment had no effect on D1 expression in the NAc shell in male and female rats (Fuentes et al., 2018). This discrepancy may be because only one subregion and not entire NAc was examined in this study. Alternatively, different

types of early life adversity could have distinct effects on D1 receptors. ELS can also affect D2 receptor expression in the NAc but typically causes an increase in this receptor. In males (females were not tested), prenatal restraint stress as well as maternal separation alone or in combination with cocaine exposure increases D2 receptor expression in the NAc (Berger, Barros, Sarchi, Tarazi, & Antonelli, 2002; Gracia-Rubio et al., 2016; Romano-López et al., 2016), but see (Majcher-Maślanka et al., 2017). A stress-induced increase in D2 receptors, assuming postsynaptic, would inhibit the NAc, which may help control increased DA influx in the NAc. Higher expression of NAc D2 receptors following ELS may drive changes in impulsivity, because, as noted, reduced D2 receptor expression is positively correlated with poor inhibitory control (Cropley, Fujita, Innis, & Nathan, 2006; Hamidovic, Dlugos, Skol, Palmer, & de Wit, 2009).

Another regulator of dopaminergic function is DAT. In humans, low levels of DAT, which could increase DA signaling, are associate with poor inhibitory control (H. Kim, 2018; Sekiguchi, Pavey, & Dean, 2019; Smith et al., 2018). ELS manipulations can be combined with animal models thought to capture aspects of psychiatric disease, such as the spontaneously hypertensive rat (SHR), which has features of ADHD, including inattention, impulsivity, and hyperactivity (Knardahl & Sagvolden, 1979; Russell, Sagvolden, & Johansen, 2005; Sagvolden, 2000; Sagvolden, Russell, Aase, Johansen, & Farshbaf, 2005; Wultz, Sagvolden, Moser, & Moser, 1990). Maternal separation in SHR increases the rate of DA clearance in the ventral striatum (Womersley, Hsieh, Kellaway, Gerhardt, & Russell, 2011). An increased rate of clearance is indicative of reductions in DAT function because less DA is being removed from the synapse. Consistent with this finding, male rats (females were not studied) that experience maternal separation show reduced DAT expression in the accumbens and display increased sensitization to amphetamine (Brake, Zhang, Diorio, Meaney, & Gratton, 2004; Meaney, Brake, & Gratton, 2002). Interestingly, female, but not male, rats exposed to maternal stress are less susceptible to methamphetamine induced decreases in striatal DAT content (Hensleigh & Pritchard, 2015). Thus, another mechanism by which ELS could impact impulsivity is via altering DAT function.

ELS also affects plasticity within the NAc (Monroy, Hernández-Torres, & Flores, 2010; Romano-López et al., 2016). Female rats that experienced prenatal stress in combination with motherless rearing have decreased expression of neuronal markers of plasticity such as synaptophysin and brain-derived neurotrophic factor in the accumbens (Burton et al., 2007). Prenatal stress with maternal separation increases dendritic MSN branching in both male and female rats (Muhammad, Carroll, & Kolb, 2012). Increased branching can provide more surface area for synaptic connections. These data illustrate that synaptic development is sensitive to different forms of ELS. What is unclear, however, is if ELS promotes inhibitory or excitatory synaptic connections. Electrophysiology data suggests male, but not female rats, exposed to LBN exhibit reductions in spontaneous excitatory postsynaptic currents (sEPSCs) in the NAc core (the shell was not assessed) (Ordoñes Sanchez et al., 2021). These findings could suggest that early life experiences can potentially reduce excitatory synapses and therefore, reduce glutamate transmission in the NAc. Reductions in glutamate transmission in the NAc is associated with reduced impulsive choice in males (Ordoñes Sanchez et al., 2021; Justin R. Yates & Bardo, 2017). These findings indicate that ELS can

alter other aspects of accumbal plasticity in addition to regulating DA which could impact impulsivity.

It is important to mention that there is a disconnect between the detail in which the NAc has been studied in the ELS field vs. the impulsivity field. The impulsivity literature has revealed distinct functions of the NAc core and NAc shell, with a stronger role for NAc core in impulsive choice and the NAc shell in impulsive action (Dalley & Ersche, 2019; J. W. Dalley & Robbins, 2017; Ito, Robbins, & Everitt, 2004). Many ELS studies, however, often focus on the entire NAc or only examine one subregion. Future ELS studies need to better incorporate core/shell assessments to further our understanding of the mechanisms by which ELS alters impulsive behavior.

7. Effects of ELS on the Cortex Can Mediate Impulsivity

The cortex also plays a role in impulsive behavior, and ELS can affect the cortex. Recall that cortical DA signaling contributes to the expression of behavioral impulsivity (Loos et al., 2010; Puumala & Sirviö, 1998; C. A. Winstanley et al., 2006; C. A. Winstanley et al., 2010). ELS alters DA innervation of the cortex (Kunzler, Braun, & Bock, 2015). For example, maternal separation causes tyrosine hydroxylase (TH)-fiber density in the OFC to be higher in male, but not female, *Octodon degus* (Kunzler et al., 2015). Given that TH is a marker for DA projections, these data suggest ELS increases dopaminergic innervation in the OFC. Interestingly, in the same study density of TH fibers in the mPFC was lower in stressed than control males with no effects found in females (Kunzler et al., 2015). These results indicate that ELS alters dopaminergic innervation in the cortex in a region-specific manner. ELS can also alter cortical DA receptors. Maternal separation in male rats (females were not tested) increased adolescent D1 expression but reduced adult D2 receptor expression on glutamatergic projection neurons from the prelimbic PFC (Brenhouse, Lukkes, & Andersen, 2013). However, in the prelimbic PFC projections specifically to the NAc, maternal separation caused a transient decrease in both D1 and D2 receptors in adolescence (Brenhouse et al., 2013). Studies on the effects of ELS on DA in the PFC are limited, and much more research in this area is warranted.

In addition to changes in cortical dopamine, cortical glutamate dysfunction is associated with impulsivity in ADHD, SUD, bipolar disorder, and preclinical models (Jochen Bauer et al., 2018; J.-N. Li, Liu, & Li, 2020; Emily R. Murphy et al., 2012; Smaragdi, Chavez, Lobaugh, Meyer, & Kolla, 2019). As an example, people with ADHD have higher glutamate in the ACC than controls and these high glutamate levels are positivity correlated with impulsivity symptoms (J. Bauer et al., 2018). ELS can affect cortical glutamate. Primates reared in adverse conditions have higher ACC glutamatergic signaling than controls (Mathew et al., 2003). Glutamatergic tone in cortical regions is modulated by local parvalbumin (PV) GABAergic interneurons (Sohal, Zhang, Yizhar, & Deisseroth, 2009; Williams, Goldman-Rakic, & Leranth, 1992). Several lines of rodent research demonstrate that ELS reduces PV neurons in the mPFC and OFC (Goodwill et al., 2018; Grassi-Oliveira, Honeycutt, Holland, Ganguly, & Brenhouse, 2016; Ohta et al., 2020). Interestingly, the effect of ELS on cortical PV neurons differs by sex and developmental stage. Maternal separation reduces PV neurons of the mPFC transiently in juvenile female rats but causes

a persistent decline of these neurons in male rats which starts in adolescents and continues into young adulthood (Grassi-Oliveira et al., 2016; Holland, Ganguly, Potter, Chartoff, & Brenhouse, 2014). In the OFC, LBN reduces PV neurons in female but not male mice (Goodwill et al., 2018). These ELS-induced changes in cortical PV have been linked to cognitive and social deficits, but they have not directly been linked to impulsivity, a gap that should be addressed in future studies. Collectively, these findings suggest that another mechanism by which ELS can alter impulsivity is by increasing cortical glutamate signaling.

8. Conclusion

How ELS affects impulsivity is just beginning to be elucidated and there remain many unanswered questions. However, the rodent literature demonstrates that ELS increases impulsive action and decreases impulsive choice. Yet, these findings are not totally aligned with human studies: while both rodent and human studies report that ELS increases impulsive action, in humans, adversity in childhood also typically increases impulsive choice (Duckworth, Kim, & Tsukayama, 2013; S. T. Kim et al., 2018; Lovallo et al., 2013). One possible explanation for why ELS effects on impulsive choice differ in the rodent versus human literature could be differences in the stressor timing and duration, and the types of stressors experienced. Most rodent models of ELS utilize one specific stress manipulation during a restricted developmental timeframe, in part, to identify sensitive windows (Molet et al., 2014; Nishi et al., 2014; Walker et al., 2017). However, stressful events experienced by children are not typically restricted to a limited developmental window (Lupien, McEwen, Gunnar, & Heim, 2009). Moreover, most children who experience ELS report multiple forms of adversity prior to adulthood (Arata, Langhinrichsen-Rohling, Bowers, & O'Brien, 2007; Green et al., 2010; Kessler et al., 2010; Katie A. McLaughlin et al., 2010; K. A. McLaughlin et al., 2012). Additionally, while most rodent models of ELS focus on some form of neglect (e.g., neglect of maternal care or physical resources), clinical studies also take into consideration stress stemming from other ELS subtypes (e.g., sexual, physical, and emotional abuse) (Katie A. McLaughlin et al., 2010; K. A. McLaughlin et al., 2012). Different types of early trauma can lead to different outcomes later in life. For instance, a meta-analysis found that childhood abuse was positively associated with the development of adult psychopathology, but not neglect stemming from caregivers unable to provide basic needs such as housing/shelter (Carr, Martins, Stingel, Lemgruber, & Juruena, 2013). Because most rodent models of ELS involve stress from neglect, they may not always capture the effects of childhood trauma in humans. One approach would be to try to develop rodent models that better capture multiple stressors for a more protracted period of development. Another approach is to study impulsivity in humans who have experienced briefer and milder forms of early adversity. Although there is some disconnect regarding impulsive choice between the rodent and human ELS studies, it does not mean the rodent research cannot be leveraged into better treatments for those suffering from conditions with impulsive choice as a feature. Using rodent models to discover mechanisms that reduce impulsivity may reveal novel treatments for disorders characterized by high impulsivity.

In conclusion, adverse experiences early in life can alter many cognitive processes, including impulsivity. Although the precise mechanisms by which this occurs are still not fully elucidated, regulation of the mesocortolimbic system by ELS clearly contributes to later

alterations in impulsive behavior. Future studies which disentangle stressor type, duration, and developmental window as well as consistently compare males and females are needed to better understand conditions that promote vulnerability vs. resilience to ELS. Leveraging these data can help improve therapeutics to treat several conditions including ADHD, bipolar disorder, and SUD.

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Highlights:

- Impulsivity is mediated by the mesocorticolimbic dopamine (DA) system
- Exposure to early life stress can alter impulsivity in adulthood
- Early life stress induces changes in the mesocorticolimbic DA system to impact impulsivity

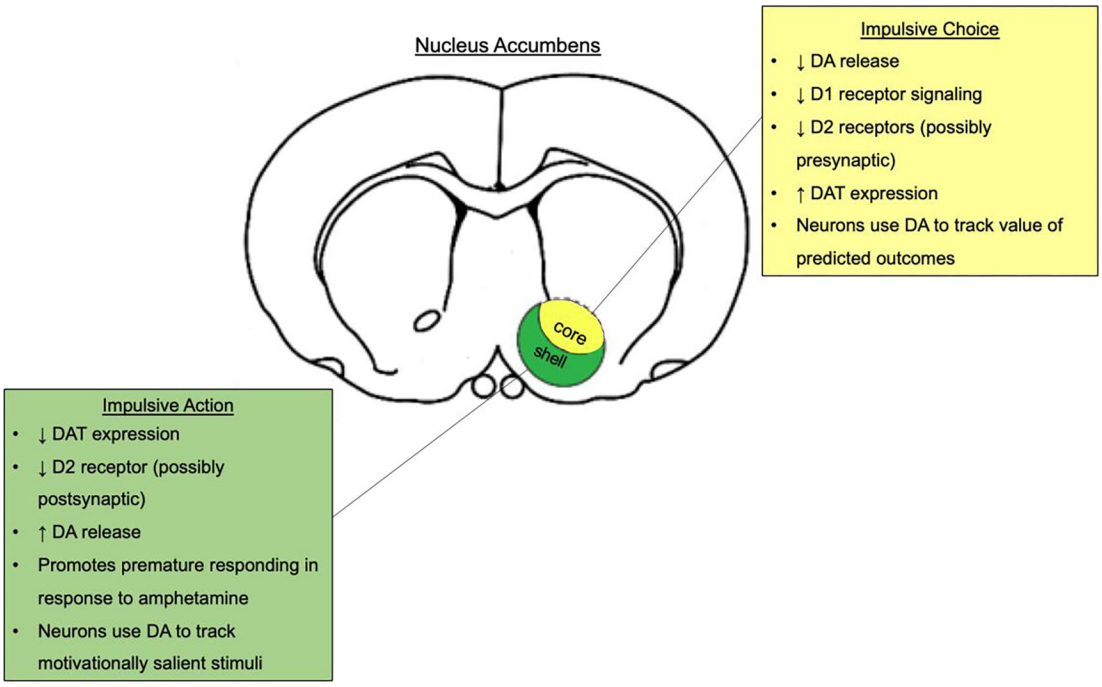

Fig. 1.

A schematic showing how the NAc core and shell regulate aspects of impulsivity. Changes in the dopaminergic system that increase DA tone in the shell promote impulsive action. In contrast, changes in the dopaminergic system that decrease DA signaling in the core promote impulsive choice. DA, dopamine; D1 receptor, dopamine 1 receptor; D2 receptor, dopamine 2 receptor; DAT, dopamine transporter.

Table 1.

Summary of ELS effects on impulsive action and impulsive choice.

Impulsivity Type	Timing	Stress Model	Effect	Citations
Impulsive Action	Prenatal	Variable	Increase	Wilson et al., 2012
Impulsive Action	Postnatal	Scarcity	Increase	Kentrop et al., 2016; Lovic, Kleen, Fletcher, & Fleming, 2011
Impulsive Choice	Prenatal	Prenatal Restraint Stress + Lead Exposure	Decrease in males, no effect females	Weston et al., 2014
Impulsive Choice	Postnatal	Scarcity	Decrease *	Ordñnes Sanchez et al., 2021; Fuentes et al., 2014; Lovic et al., 2011
Impulsive Choice	Postnatal	Maternal Separation + Ethanol Exposure	Increase	Gondré-Lewis et al., 2016

* indicates that the effect is more pronounced in one sex than the other depending on the type of scarcity manipulation (artificial rearing, maternal separation, LBN).