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Which came first: cannabis use or deficits in impulse control?

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Abstract

Impulse control deficits are often found to co-occur with substance use disorders (SUDs). On the one hand, it is well known that chronic intake of drugs of abuse remodels the brain with significant consequences for a range of cognitive behaviors. On the other hand, individual variation in impulse control may contribute to differences in susceptibility to SUDs. Both of these relationships have been described, thus leading to a "chicken or the egg" debate which remains to be fully resolved. Does impulsivity precede drug use or does it manifest as a function of problematic drug usage? The link between impulsivity and SUDs has been most strongly established for cocaine and alcohol use disorders using both preclinical models and clinical data. Much less is known about the potential link between impulsivity and cannabis use disorder (CUD) or the directionality of this relationship. The initiation of cannabis use occurs most often during adolescence prior to the brain's maturation, which is recognized as a critical period of development. The long-term effects of chronic cannabis use on the brain and behavior have started to be explored. In this review we will summarize these observations, especially as they pertain to the relationship between impulsivity and CUD, from both a psychological and biological perspective. We will discuss impulsivity as a multi-dimensional construct and attempt to reconcile the results obtained across modalities. Finally, we will discuss possible avenues for future research with emerging longitudinal data.

Keywords

Addiction; Cannabis; Impulsivity

1. Introduction

While the word *impulsive* has a straightforward enough definition according to the Cambridge dictionary, "acting or done suddenly without any planning or consideration of the results," there is far less clarity when it comes to describing the psychological term

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impulsivity (Press, 2008). Impulsivity is a multidimensional construct with separable domains. Consequently, a number of definitions and theoretical conceptualizations have been proposed (Bakhshani, 2014, Lee et al., 2019, MacKillop et al., 2016, Stahl et al., 2014). Despite an overall lack of consensus on the definition, impulsivity is a hallmark for numerous impulse control disorders (e.g. intermittent explosive disorder, oppositional defiant disorder, and klepto- and pyromanias) in addition to serving as a diagnostic criterion for other mental disorders like attention-deficit/hyperactivity disorder (ADHD) and antisocial and borderline personality disorders. Central to this review, there are high rates of co-occurrence between impulse control disorders and substance use disorders (SUDs) (Fontenelle et al., 2011). Indeed, it is often repeated that a hallmark of SUDs is an inability to control the impulse to use drugs even in the face of severe negative consequences.

As with other abused drugs, most individuals who try cannabis will not transition to daily drug use or abuse. Public perception is growing more favorable towards cannabis use (Carliner et al., 2017, Pacek et al., 2015), but for a subset of people chronic use can have severe negative psychological and physical consequences including addiction. Cannabis is one of the three most frequently used drugs of abuse in the United States (US) along with alcohol and tobacco/nicotine (SAMHSA, 2019). Two common misconceptions are that cannabis lacks addiction liability, and that cannabis use disorder (CUD) is rare compared to other SUDs. In recent years, there has been a significant increase in the numbers of young adults showing patterns of frequent use in the US (SAMHSA, 2019). In the last 10 years, the percentage of delta-9-tetrahydrocannabinol (THC, the primary psychoactive chemical in cannabis) in seized cannabis has nearly doubled (Chandra et al., 2019). Correspondingly, there has been an increase in the incidence of CUD measured across multiple studies (Hasin, 2018). Current estimates from US national data place the incidence of meeting diagnostic criteria for CUD at approximately 20% of lifetime users illustrating that it is not a rare phenomenon (Hasin, 2018).

There are many theories about why some individuals develop SUDs and others do not. Drug access represents a primary risk factor (Gillespie et al., 2009). The changing legislative landscape in the US and beyond suggests that cannabis availability will only increase in the coming years. Beyond availability, this review explores one potential explanation for individual differences in susceptibility to cannabis misuse/CUD by examining the relationship with impulsivity. Research in animal models indicates that high impulsivity is correlated with substance abuse susceptibility (Jentsch et al., 2014). Moreover, clinical research suggests that impulsivity levels can influence treatment response and relapse (Bentzley et al., 2016, Loree et al., 2015). Most of this research has centered on alcohol and stimulant use, and indeed strong associations have been described in terms of these abused substances (Dick et al., 2010, Perry and Carroll, 2008). The development of CUD, as for other SUDs, is associated with a constellation of risk factors, but the link between impulsivity and cannabis use warrants further investigation.

2. Cannabis use disorder

The most recent version of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) provides the currently accepted diagnostic criteria for CUD nested under

the category of “Substance-related and addictive disorders.” The DSM-5 definition of CUD is “a problematic pattern of cannabis use leading to clinically significant impairment or distress” as manifested by fulfilling 2 or more of the 11 established criteria in a 12 month span (APA, 2013). An unweighted criteria count is used to overlay a severity parameter: 2–3 criteria = mild, 4–5 criteria = moderate and 6+ criteria = severe CUD. Prevalence of past year cannabis use in the US for individuals ages 12+ is reported at 15.9% (SAMHSA, 2019). Although it has previously been touted that approximately 9% of regular of cannabis users progress to DSM-IV cannabis dependence (Lopez-Quintero et al., 2011), updated national data finds that the lifetime cumulative probability of transition to DSM-5 CUD is estimated to be 27% (inclusive of mild, moderate and severe) (Feingold et al., 2020). Comparison studies suggest that diagnosis of CUD is similar under DSM-5 criteria compared to abuse and dependence under DSM-IV (SAMHSA, 2016), suggesting that increased prevalence of CUD over the past decade is likely reflective of other factors such has increased access following legalization and higher THC potency rather than changes in diagnostic criteria (see Box 1).

Many biological, psychological, social, and environmental factors can increase risk for transitioning from cannabis use to CUD. Male sex, other substance use, comorbid psychopathology, earlier age of initiation, and peer influences are primary risk factors for subsequently developing CUD (Courtney et al., 2017). Additionally, cannabis users report a variety of motives for initiation and maintenance of use (e.g., coping, conformity, social, expansion). There is evidence that using cannabis to cope with negative affect is associated with more frequent use and negative outcomes (Buckner, 2013, Moitra et al., 2015, Sofis et al., 2020). Researchers have made various attempts to assemble psychological profiles of cannabis users. One model suggests that four personality factors (i.e., anxiety sensitivity, introversion/hopelessness, sensation seeking, and impulsivity) are associated with elevated risk for SUDs, with distinct factors being related to preference for or susceptibility to particular drugs (Woicik et al., 2009). The Substance Use Risk Profile Scale (SURPS) is a psychometric scale specifically designed to assess association with SUDs, like motives for cannabis use, across those four dimensions (Woicik, Stewart, 2009). For example, high sensation seeking was related to expansion motives (e.g. “be more creative,” “expand awareness”) while anxiety sensitivity and introversion/hopelessness were associated with coping motives (Hecimovic et al., 2014). Impulsivity showed association with the coping motive, “to help when feeling down,” as well as drug availability motives (i.e. “easier to get than other drugs”) (Hecimovic, Barrett, 2014). This study and others (Chabrol et al., 2012) suggest substantial heterogeneity among cannabis users especially when considering broad non-clinical populations. The Hecomovic et al (2014) investigation did not correlate these factors with cannabis use frequency or cannabis-associated problems, but it may be possible to further refine some of these profiles based on these distinctions.

Cannabis use disorder is highly comorbid with other substance use and psychiatric disorders. Most adults with CUD also have an alcohol use disorder (59% men; 60% women) or another drug use disorder (14% men; 18% women) (Kerridge et al., 2018). Common psychiatric co-diagnoses include mood disorders (33% men; 49% women), anxiety disorders (23% men; 36% women), and personality disorders (48% men; 59% women). Adults with the hyperactive-impulsive subtype of ADHD are more than twice as likely to meet diagnostic

criteria for CUD (De Alwis et al., 2014). Importantly, both other substance use and many psychiatric disorders are associated with impulsivity (Coskunpinar et al., 2013, Kulacaoglu and Kose, 2018, Stautz and Cooper, 2013, Weafer et al., 2014), suggesting consideration of comorbidities is important when seeking to understand distinct effects of cannabis use.

Cannabis use is becoming more widespread, but individual motives, patterns of use, and various substance use and psychiatric comorbidities highlight the immense heterogeneity in cannabis users. These individual differences might account for some of the variability and/or incongruity observed in the examined investigations. Still, one or more common underlying vulnerability factors may explain a common liability for moderate to severe CUD.

3. Defining the constructs of impulsivity

Despite over a century of research, there is still no unified framework nor agreed upon psychological definition for impulsivity. Numerous personality theories have included the concept of impulsivity (Cloninger et al., 1993, Eysenck and Eysenck, 1977, Zuckerman and Kuhlman, 2000). In this review, we propose that impulsivity can be measured as a trait or a state. Impulsive trait is relatively stable across time, but impulsive state is characterized by variability in impulsivity levels that depend on external environmental or internal proprioceptive conditions. Impulsivity as a state is considered a normal dimensional behavior as well as pathological construct of several diagnosable mental disorders including ADHD, antisocial and borderline personality disorders, and SUDs. Trait impulsivity, often measured through self-report personality assessments, is based on internal perceptions of behavior that can be evaluated on separable factors. Sensation seeking is a related but non-overlapping construct defined as the propensity to pursue novel, diverse and thrilling experiences and the willingness to take risks in that pursuit (Zuckerman, 1979). We include sensation seeking in this review because the concepts appear to be both operationally and biologically correlated (Hur and Bouchard, 1997), though it is not our intention to conflate the two (Cyders et al., 2007). Each of these scales in this non-exhaustive list (Table 1) has been used to correlate impulsivity with SUDs. This inherent heterogeneity in terms of the definition of impulsivity and the various dimensions that comprise it likely contribute to some of the inconsistency in the literature with respect to associations with CUD and other SUDs– especially if only certain domains ultimately capture the association.

Impulsivity is also assessed through tasks that measure overt behavior. Behavioral assessments measure different aspects of impulsivity akin to the diversity of survey measures. One useful organizational framework that has been put forth separates impulsive choice (inability to delay gratification) from impulsive action (impaired response inhibition) and self-reported impulsive personality traits (MacKillop, Weafer, 2016). Lee and colleagues proposed a slightly different framework based on their meta-analysis that centers on three neurocognitive components: Response inhibition, reward discounting, and disadvantageous decision-making (Lee, Hoppenbrouwers, 2019). In agreement with Robbins and Dalley, who wrote a chapter in the literal book *Impulsivity: How Time and Risk Influence Decision Making*, “such distinctions, although useful, do not always capture the relevant dimensions of impulsivity and their neuropsychological basis.” Still, some of this terminology is used here because it is easily understood and aids in translating findings between humans and

animal models (Table 2). Conveniently, these rodent models have allowed researchers to more directly study the basis of inter-individual variation in impulsivity-related behaviors by selecting out and even breeding animals at the behavioral extremes (Isherwood et al., 2017).

Enticott and Ogloff argue that impulsivity is neither a single or multidimensional construct but rather an assemblage of "characteristically similar behaviors that are determined by one of a number of underlying constructs" (Enticott and Ogloff, 2006). In support, the prevailing literature indicates that there is little correlation between various measures of impulsivity. For example, utilizing a hypothesis-driven factor analysis that examined >1000 control subjects with multiple laboratory tasks (DD, GNG, SST, CPT) and survey measures (BIS-11, UPPS-P), it was confirmed that a three-factor model provided the best fit of the data; however, these three underlying factors were not highly related (MacKillop, Weafer, 2016). While impulsive personality traits captured by the two survey measures showed very modest associations with impulsive behaviors, there was a complete lack of relationship between task measures for impulsive choice versus impulsive action (MacKillop, Weafer, 2016). This replicated a previous study performed on a much smaller scale dissociating behavioral dimensions of impulsivity (Reynolds et al., 2008). This dissociation was preserved across species (rats vs humans), but in this case, the human subjects self-reported impulsivity (BIS-11) showed no association with their behavioral measures (Broos et al., 2012). Comprehensive meta-analyses confirm weak to moderate correlations, if any, between impulsivity self-report measures and laboratory tasks (Cyders and Coskunpinar, 2011, Sharma et al., 2014). Moreover, distinct dimensions of impulsivity are being tapped by the separate survey measures and laboratory tasks, although, as mentioned, there is not universal agreement upon a dimensional model (Cyders and Coskunpinar, 2011, Meda et al., 2009, Sharma, Markon, 2014). Some of the discrepancy between studies could be accounted for by methodological differences in data reduction, small sample sizes, and dissimilar demographics of study populations. For instance, the latent structure of impulsivity may not be identical in healthy controls and individuals in clinical populations (Meda, Stevens, 2009). Importantly, both laboratory tasks and survey measures separately show association with real-world measures of daily life impulsivity like gambling and risky sexual behavior (Sharma, Markon, 2014). There has been some effort made to improve the concordance between self-report and laboratory measures of impulsivity (Ellingson et al., 2018), but many would argue that the lack of concordance is a feature rather than a bug allowing investigators to build more powerful models incorporating state and trait information.

The primary point of emphasis here is the importance of specifying which construct(s) of impulsivity is being applied to form which conclusion. Because impulsivity is not a unitary construct, it complicates the association with CUD. Similarly "addiction" is not a unified condition, nor is every cannabis user the same (Pearson et al., 2017).

4 The neural basis of impulsivity

4.1 The neuroanatomy of impulsivity

The prefrontal cortex (PFC) is the brain structure most often associated with behavioral inhibition and decision making and consequently implicated in impulsivity (Kim and Lee, 2011). The PFC is divided into numerous subregions each with their own functional

specializations and embedded within a larger network structure. Most studies describe negative relationships between cortical (and subcortical) gray matter volume and survey measures of impulsivity (Holmes et al., 2016, Korponay et al., 2017, Kumari et al., 2009, Matsuo et al., 2009) but see (Cho et al., 2013, Gardini et al., 2009). One of the most consistent findings is a negative relationship with orbitofrontal cortex (OFC) volume (Korponay, Dentico, 2017, Kumari, Barkataki, 2009, Matsuo, Nicoletti, 2009). Measurements of gray matter volume vary based on both thickness and surface area fluctuations; consequently, it may not be the most sensitive readout and this potentially contributes to some inconsistency in results. Akin to volumetric analyses, negative correlations are observed between cortical thickness and impulsivity (Kubera et al., 2018b, Schilling et al., 2012). Few studies to date have examined the relationship between impulsivity and cortical surface area, although Kubera et al. failed to discern any relationship in healthy controls (Kubera, Schmitgen, 2018b).

Functional analyses like resting state functional connectivity (RSFC) provide additional information about the neural networks underlying impulsivity. Resting state functional magnetic resonance imaging (rs-fMRI) measures the degree of correlated activity between spatially distributed brain regions with the objective of characterizing functional networks when the brain is at rest. Seed-based methods reveal distinct functional networks correlated with impulsivity subscales centered on identified regions of interest (ROIs) (Angelides et al., 2017, Korponay, Dentico, 2017). For example, subcortical ROIs in the basal ganglia and midbrain identified separate networks associated with the BIS motor versus the BIS non-planning scales (Korponay, Dentico, 2017). Similarly, within-subjects analysis identified separate networks associated with behavioral tasks for impulsive choice (DD) versus impulsive action (SST) utilizing the frontal pole and inferior frontal gyrus as seeds (Wang et al., 2016). A recent study applied an independent component analysis to rs-fMRI data identifying three discrete networks associated with trait impulsivity without the *a priori* selection of ROIs. They identified a right frontoparietal network including OFC and dorsolateral PFC (dlPFC) associated with all three BIS domains (attentional, motor and non-planning) and striatal and medial frontal/cingulate networks correlated selectively with the motor domain (Kubera et al., 2018a). It is encouraging that their non-biased results significantly map onto our existing neuroanatomical knowledge of impulsivity networks.

Experiments performed in preclinical animal models exploiting laboratory tasks that parallel human behaviors have aided in the validation of these neural networks. Investigators can directly probe the involvement of specific brain regions using lesion/inactivation, pharmacology, and more recently chemo- and optogenetic manipulations. Distinct neural processes contributing to different forms of impulsivity can thus be ascertained. For example, transient pharmacological inactivation of the ventral medial PFC (prelimbic and infralimbic) impaired impulse control in the 5CSRTT but did not affect DD in rats (Feja and Koch, 2014). Traditional neuroanatomical disconnection studies employing contralateral lesions to ventral PFC and ventral hippocampus further implicated this network in inhibitory response control in the 5CSRTT (Chudasama et al., 2012). Inactivation of anterior cingulate (ACC) or dorsal prelimbic cortices increased stop signal reaction time, another index of impulsive action, with selective contribution of noradrenergic signaling in the dorsal prelimbic (Bari et al., 2011). Lesions of the ACC also promoted disinhibited responding in a

rodent touch-screen CPT without affecting attentional processing (Hvoslef-Eide et al., 2018). Lesion or inactivation of the medial PFC increased risky decision making in the rGT (Paine et al., 2013, Zeeb et al., 2015).

Parallel to the human structural and functional data, significant research has focused on the role of OFC in impulsivity-related behaviors in animal models, but studies have yielded inconsistent results. Lesion of the basolateral amygdala or OFC (or their disconnection) impaired acquisition of the rGT, but with additional training performance reached equivalence with sham-operated controls (Zeeb and Winstanley, 2011, 2013). Neither inactivation nor lesion of OFC disrupted decision-making on the rGT after rats were trained (Zeeb, Baarendse, 2015, Zeeb and Winstanley, 2011); in contrast, basolateral amygdala lesions were sufficient to increase risky choice (Zeeb and Winstanley, 2011). In the DD task, OFC lesion or inactivation has been shown to increase, decrease or have no effect on impulsive choice (Winstanley et al., 2004b)(Mar et al., 2011, Stopper et al., 2014), but some studies offer clues to disentangle this ambiguity. For instance, basal levels of impulsivity and differences in incentive salience attribution to reward cues differentially influenced the effects of OFC inactivation on DD (Zeeb et al., 2010). Moreover, functional heterogeneity of anatomical sub-regions within the OFC differentially impact learning and decision-making related behaviors, and many studies fail to specify which OFC sub-regions are targeted (Izquierdo, 2017). Mar and colleagues were the first to demonstrate a dissociable role for medial and lateral OFC in the rodent, wherein lesion of the medial OFC decreased and lesion of the lateral OFC increased impulsive-like responding in the DD task relative to sham controls (Mar, Walker, 2011). These results align well with human neuroimaging data supporting the ß-∂ model of intertemporal choice proposed by McClure and colleagues (McClure et al., 2004). Other recent evidence suggests that this may be an oversimplification of the complex role of the OFC in impulsivity (Sellitto et al., 2010).

Subcortical regions are also important regulators of impulsivity. The dorsomedial striatum and subthalamic nucleus mediate impulsive action inhibtion in the SST and 5CSRTT (Eagle and Baunez, 2010). The nucleus accumbens (NAc) core plays a complex role in regulating impulsive choice in the DD task. Chemogenetic activation of designer receptors exclusively activated by designer drugs (DREADDs) have been used to bidirectionally modulate the medial OFC-NAc core projection in rats (Wang et al., 2019). Activation of this pathway decreased delay discounting in high impulsive rats; inactivation increased delay discounting in low impulsive rats (Wang, Yue, 2019) in line with most prior NAc lesion and inactivation studies (Cardinal et al., 2001, Valencia-Torres et al., 2012) but see (Moschak and Mitchell, 2014). Interestingly, lesion of the entire NAc (core and shell) decreased delay discounting, again highlighting important neuroanatomical sub-region effects (Acheson et al., 2006). On the whole, these studies highlight distinct but not mutually-exclusive networks related to impulsivity constructs (Eagle and Baunez, 2010, Robbins and Dalley, 2017). Notably, these circuits overlap with those implicated in reward and development of SUDs (Crews and Boettiger, 2009).

4.2 Neurochemical basis of impulsivity

4.2.1 Serotonin—Deficits in 5-hydroxytryptamine (5-HT) neurotransmission tend to correlate with increased impulsivity in humans and animal models (Mavrogiorgou et al., 2017, Winstanley et al., 2004a). There is ample support for a role for 5-HT signaling in waiting impulsivity with perhaps a less well-defined role in stopping impulsivity or tasks that measure impulsive choice. For example, global 5-HT depletion in rats increased premature responding without altering performance accuracy in the 5CSRTT (Harrison et al., 1997), impaired measures of waiting but not stop reaction time in the SST (Eagle et al., 2009), and did not alter DD (Winstanley, Dalley, 2004a). Conversely, optogenetic activation of 5-HT neurons in the dorsal or median raphe nucleus of transgenic mice decreased premature responding in a 3CSRTT in further support of a positive regulatory role of serotonin for promoting waiting (Ohmura et al., 2020). In healthy control human subjects, central 5-HT reduction via acute tryptophan depletion increased premature responding in a 4CSRTT (Worbe et al., 2014), but did not alter stop reaction time (Clark et al., 2005). However, conflicting results were obtained when delay discounting was assessed in humans using either a reward delay questionnaire (no effect, (Worbe, Savulich, 2014)) or a computerized task with actual delays (increased discounting, (Schweighofer et al., 2008)). Consistent with a negative correlation between 5-HT transmission and impulsive-like behavior, a positive relationship was reported for serotonin transporter (SERT) function in the OFC with DD and a behavioral measure of negative urgency in rats (Darna et al., 2015, Yates et al., 2015). Despite this proposed relationship with SERT, selective serotonin reuptake inhibitors (SSRIs) have demonstrated poor and inconsistent effects on impulsivity in humans and animal models (Macoveanu et al., 2013, Mori et al., 2018).

The large receptor family (5-$HT_{1–7}$) further complicates elucidating the role of 5-HT in impulsivity. On the whole, 5-HT_{2A} receptor agonism increases and antagonism decreases impulsive action (Fink et al., 2015, Silveira et al., 2020). In contrast, 5-HT_{2C}-specific modulations produce inverse behavioral effects (Higgins et al., 2020a, Silveira, Wittekindt, 2020) pointing to opposing roles for 5-HT_{2A} and 5-HT_{2C} receptors. A greater ratio of 5-HT_{2A}:5-HT_{2C} but reduced protein complex in mPFC synaptosomes was associated with higher premature responding in a 5CSRTT (Anastasio et al., 2015). Fewer reports have examined the contribution of these receptor subtypes to impulsive action, but in at least one study 5-HT_{2C} antagonism decreased DD (Paterson et al., 2012). Genetic and pharmacologic evidence also points to the involvement of 5-HT_{1A} and 5-HT_{1B} receptors in regulating various forms of impulsivity (Korte et al., 2017, Nautiyal et al., 2017). Very little is known regarding the involvement of other 5-HT receptors, but individual 5-HT receptor subtypes influence unique biochemical signaling pathways.

4.2.2 Dopamine—Many medications prescribed to treat ADHD, characterized by impulsivity, act by increasing dopamine levels in the brain (Connolly et al., 2015). Despite their widespread use in ADHD, psychostimulant drugs produce mixed effects on impulsivity in control subjects. For example, in rodents and humans amphetamine tends to improve performance and reduce impulsivity on the SST, DD, and CPT variants (Baarendse and Vanderschuren, 2012, de Wit et al., 2002, Dolder et al., 2018, MacQueen et al., 2018b), but consistently increases impulsive action in the 5CSRTT in rodents (Baarendse and

Vanderschuren, 2012, Higgins et al., 2020b, Robbins, 2002). Of course, amphetamine is not selective for the dopamine transporter (DAT), but DAT blockers reproduced those effects (Baarendse and Vanderschuren, 2012). At the other end of the spectrum, a large segment of Parkinson's disease patients treated with dopamine agonists develop impulse control disorders and compulsive behaviors with long-term dopamine agonist treatment (Grall-Bronnec et al., 2018). Thus an inverted U-shaped relationship between impulsivity and optimal dopamine concentration is suggested, akin to what has previously been established for dopamine actions on working memory and cognition (Cools and D'Esposito, 2011). Individual differences in self-report and task-based measures of impulsivity in healthy human subjects correlated with variation in dopaminergic function including dopamine synthesis capacity and DAT availability (Smith et al., 2018, Smith et al., 2016). Baseline impulsivity moderated the effects of L-DOPA augmentation in healthy controls on delay and probability discounting such that high-impulsive individuals become less impulsive and low-impulsive individuals became more impulsive (Petzold et al., 2019).

Acute dopamine loss (~30% decrease) in healthy human subjects impaired impulse suppression but not impulse activation in a Stroop-like Simon Task (Ramdani et al., 2015). In rodents, DREADDs have been used to temporarily inhibit or activate midbrain dopamine neurons. Inhibition of dopamine neurons in the ventral tegmental area (VTA) decreased impulsive-like responding in the 5CSRTT in mice (Fitzpatrick et al., 2019), but chemogenetic activation of VTA or substantia nigra selectively impaired attention on this same task in rats (Boekhoudt et al., 2017). In contrast to acute inhibition, non-reversible dopamine lesions increased delay discounting in adult rats (Tedford et al., 2015) and produced an ADHD-like phenotype complete with deficits in attention and increased premature responding in the 5CSRTT in neonatally lesioned mice (Bouchatta et al., 2018). D2/D3 availability, especially in the striatum and midbrain, has been linked to interindividual differences in basal impulsivity with a negative association commonly identified in humans and animals (Barlow et al., 2018, Buckholtz et al., 2010, Jupp et al., 2013) although a recent meta-analysis of human subjects studies failed to find correlations in non-clinical human subjects (Castrellon et al., 2019). Still, site-specific behavioral pharmacology has validated the importance of signaling at specific dopamine receptors within the NAc, mPFC, and OFC in regulation of impulsivity-related behaviors (Besson et al., 2010, Moreno et al., 2013, Pardey et al., 2013).

4.2.3 Norepinephrine—The selective norepinephrine reuptake inhibitor atomoxetine, commonly prescribed for ADHD, also decreases impulsivity in animals and control human subjects (Chamberlain et al., 2009, Fernando et al., 2012). Atomoxetine decreased premature responding in the 5CSRTT in rodents with the NAc shell identified as a key site of action (Benn and Robinson, 2017, Economidou et al., 2012) and improved stop reaction time in rats and humans (Bari et al., 2009, Chamberlain et al., 2006). Likewise, the alpha-2 adrenergic receptor agonist guanfacine decreased premature responding in the 5CSRTT in rats (Fernando, Economidou, 2012). On the other hand, chemogenetic inhibition of the locus coeruleus increased premature responding on 5CSRTT in mice, but only under more demanding conditions (Fitzpatrick, Runegaard, 2019). In comparison, the pharmacological stressor and alpha-2-adrenergic receptor antagonist yohimbine shows dissociable effects on

different forms of impulsivity. Yohimbine improved stop reaction time in control human subjects when baseline sensation seeking was controlled for (Herman et al., 2019) akin to a baseline-dependent effect in rodents (Schippers et al., 2016). Yet yohimbine increased DD in rats (Schippers, Schetters, 2016) with no effect observed in humans (Herman, Critchley, 2019). Yohimbine also increased impulsive action in an Immediate Memory Task, a CPT variant, in humans or the 5CSRTT in rats (Mahoney et al., 2016, Swann et al., 2013). This effect on 5SCRTT was dependent on multiple neurotransmitter systems interaction because no single receptor antagonist was able to reverse it (Mahoney, Barnes, 2016). It is difficult to interpret any of these findings in a vacuum because atomoxetine and yohimbine influence the levels of other monoamines (Brannan et al., 1991, Bymaster et al., 2002).

4.2.4 Glutamate and gamma-aminobutyric acid (GABA)—As the primary excitatory and inhibitory neurotransmitters in the brain, glutamate and GABA are essential for proper brain function. Compared to the monoamine neurotransmitters there is less research into their specific contributions to impulsivity, especially in non-clinical populations. A positive correlation between glutamate levels in the ACC and BIS total score was reported (Hoerst et al., 2010), and a similar association between dorsal ACC glutamate levels and delay discounting was mediated by RSFC of the ACC with the midbrain (Schmaal et al., 2012). GABA levels in the dlPFC were negatively correlated with negative urgency on the UPPS in healthy adult males (Boy et al., 2011). Similarly, GABA/creatine was lower in the ACC of individuals with higher BIS total scores and those showing more marked motor impulsivity in a GNG task (Silveri et al., 2013). In contrast to the aforementioned study (Hoerst, Weber-Fahr, 2010), there was no relationship between ACC glutamate and BIS scores (Silveri, Sneider, 2013), but relatively small sample sizes and significant differences in the age and gender make-up of their study populations may have contributed to this difference. Preclinical models provide additional insight into the role of glutamate and GABA in regulation of impulsivity-related behavior. High impulsive rats displayed lower $GABA_A$ receptor binding in ACC and reduced expression of the glutamate decarboxylase (GAD) synthetic enzyme in NAc core (Caprioli et al., 2014, Jupp, Caprioli, 2013). Experimentally reducing $GAD_{65/67}$ levels in the NAc of low-impulsive rats increased their premature responding on the 5CSRTT (Caprioli, Sawiak, 2014). Specific N-methyl-d-aspartate (NMDA) receptor subunit expression patterns in mPFC correlated with premature responding in a 1CSRTT (Davis-Reyes et al., 2019). Systemic administration of NMDA antagonists increased impulsivity in 5CSRTT but decreased impulsive choice in a DD task (Higgins et al., 2016). Similar dissociable effects were reported for allosteric modulators of metabotropic glutamate receptors (Isherwood et al., 2015, Isherwood, Robbins, 2017). Altogether increased glutamate levels in frontal cortical regions seem to positively correlate with trait impulsivity. The opposite relationship may hold true for GABA.

4.2.5 Endocannabinoid system—Emerging evidence supports a direct link between the endocannabinoid system and impulsivity. For example, in healthy control subjects the density of the CB_1 receptor, the primary cannabinoid receptor in the brain, was negatively correlated with self-reported novelty seeking (Van Laere et al. 2009). Administration of a selective CB_1 receptor antagonist, rimonabant, improved inhibitory control in the 5CSRTT while not affecting performance on the SST or a delayed reward task in rats (Pattij et al.,

2007). At least one study found that rimonabant increased delay discounting in rats (Boomhower and Rasmussen, 2014). In another set of rodent studies, a cost-benefit T-maze was used to assess delay- or effort-based decision establishing dissociable roles for ACC and OFC (Khani et al., 2015). CB_1 activation in ACC with arachidonly-2'-chloroethylamide, another synthetic agonist, impaired effort based decision making while CB_1 activation in OFC promoted impulsive choice in delay-based decisions (Khani, Kermani, 2015). Rats with a mutation in the cannabinoid receptor 1 gene (*CNR1*) gene resulting in gain of function of the CB_1 receptor displayed increased impulsivity in a DD task alongside a host of other behavioral phenotypes said to be reminiscent of adolescent-like behavior (increases in risk taking, peer interaction, and reward sensitivity) (Schneider et al., 2015). Translating these findings to humans, a couple of candidate gene studies have identified associations between single nucleotide polymorphisms (SNPs) in *CNR1* and impulsivity or ADHD (Ehlers et al., 2007, Lu et al., 2008).

5. Impulsivity and cannabinoids

5.1 Impulsivity as a risk factor for cannabinoid use

5.1.1 Trait impulsivity and cannabinoid use—Trait impulsivity is consistently implicated as a risk factor for both cannabis use and cannabis-related problems (Bidwell et al., 2013, Day et al., 2013, Lopez-Vergara et al., 2019). Certain impulsive personality traits are evident in early development. Indeed, longitudinal cohort studies have demonstrated that temperamental qualities observed as early as three years of age predict personality traits and psychiatric diagnoses later in development (Caspi, 2000, Caspi et al., 1996). Within this framework, individual differences in trait impulsivity may be treated as relatively stable risk factors for SUDs and other psychiatric disorders. However, more recent evidence suggests that personality traits are not in fact as stable across the lifespan. Impulsivity and sensation seeking, for example, appear to undergo gradual age-related decline into early adulthood (Harden and Tucker-Drob, 2011). Individual differences in the rate of decline in impulsivity are associated with variable escalation in cannabis and other substance use (Quinn and Harden, 2013). In a study that further characterized impulsivity trajectories, distinct sex-dependent trajectories of impulsivity during early adolescence showed differential associations with substance use including cannabis with two trajectories identified in males and five in females (Martinez-Loredo et al., 2018). The "early increasing" trajectory predicted cannabis use for females and the "increasing" trajectory for males. (Martinez-Loredo, Fernandez-Hermida, 2018). Thus, individual differences in both baseline impulsivity as well as maturational changes in impulsivity (increases or maintenance of elevated levels versus normal developmental decline) may interact to influence vulnerability to SUDs.

Some of the strongest evidence in support of a vulnerability model comes from prospective longitudinal studies examining early trait impulsivity and later cannabis use. In one such analysis, baseline impulsivity was assessed in 8^{th} graders, and cannabis use behaviors recorded on follow-up from 9^{th}-12^{th} grade (Felton et al., 2015). Both self-report (B-SSS and EIS) and laboratory measures (Balloon analogue risk task-youth, BART-Y) of impulsivity were associated with increased cannabis use over time, although the two domains showed no

correlation with each other. Childhood hyperactivity-impulsivity as a subtype of ADHD predicted initiation of substance use and later cannabis abuse/dependence in adolescents followed from ages 11–18 (Elkins et al., 2007). Logistic regression revealed an association between impulsivity (EIS) and daily cannabis use in another study that followed participants from grade 7 through age 20 (Dugas et al., 2019). One caveat of this last study is that impulsivity was not measured until the grade 10–11 assessment, but the average age of first cannabis use was ~15 years. Many users would have already initiated use before impulsivity was assessed, therefore the predictive nature of the relationship is less certain. Prospective longitudinal studies of sensation seeking find a similar relationship. Sensation seeking in 4^{th}-5^{th} grade elementary students predicted cannabis use in 11^{th}-12^{th} grade (Hampson et al., 2008). This relationship held true for an all-male sample of late-onset (19+) cannabis users (Haug et al., 2014). Similarly, a 20-month study of adolescents enrolled in 9^{th} grade found an association between sensation seeking and cannabis use employing the SURPS (Malmberg et al., 2012). Importantly, the SURPS subscales (i.e., anxiety sensitivity, introversion/hopelessness, sensation seeking, and impulsivity) have been validated against other relevant personality measures including the BIS-11 and the SSS (Schlauch et al., 2015). In one of the first reports to examine the predictive role of SURPS, impulsivity did not predict early cannabis use despite being highly related to sensation seeking which did (Malmberg, Kleinjan, 2012). The analysis suggested a suppression effect when both impulsivity and sensation seeking were included in the model, but even when recomputed without sensation seeking, a relationship between impulsivity and cannabis use did not emerge (Malmberg, Kleinjan, 2012). However, in other samples, both impulsivity and sensation seeking have shown prospective predictive relationships with cannabis use (Newton et al., 2016). This variability could reflect subtle cultural differences in subject populations or highlight the limitations of the SURPS as a predictive instrument.

In cross-sectional studies, trait impulsivity is associated with age of use onset, frequency of use, and cannabis-related problems. Studies of adolescents have consistently reported relationships between impulsivity and cannabis related outcomes (Dougherty et al., 2013, Haas et al., 2018, VanderVeen et al., 2016). In college student populations, impulsivity is reliably associated with cannabis use and cannabis use problems (Pearson et al., 2018, Phillips et al., 2018). In one study where participants rated childhood and current symptoms on the Current Symptom Scale for ADHD, childhood hyperactivity-impulsivity was associated with earlier onset of cannabis use, and current or childhood inattention was associated with more severe cannabis related problems (Bidwell et al., 2014). In another sample of collegiate underclassmen, impulsivity moderated the positive relationship between cannabis use frequency and cannabis related problems (Simons and Carey, 2002). These study populations, though convenient, may not be particularly representative of the general population especially in terms of education and socio-economic status. In more representative samples of adolescents and young adults, impulsivity has been associated with lifetime incidence of cannabis use, increased past-12 month frequency of cannabis use and increased risk for the development of DSM-IV CUD (Blanco et al., 2014, Lee-Winn et al., 2018). Likewise, a large Danish national survey of youth reported a positive association between urgency on the UPPS-P impulsiveness scale and problem cannabis use (Rømer Thomsen et al., 2018). In a mixed sample of inpatient substance users, the SURPS scale

revealed that impulsivity was related to frequency of cannabis use, and sensation seeking was related to approach motivation for cannabis in the form of cue reactivity ratings (Schlauch, Crane, 2015). Finally, elevated impulsivity (BIS-11) and sensation seeking (SSS) were observed in cannabis dependent patients relative to controls even after an extended abstinence period (Delibaş et al., 2018).

Not all cross-sectional data reveal elevated impulsivity among cannabis users. For instance, frequent cannabis users surprisingly scored relatively low overall on measures of trait impulsivity (BIS and Impulsive Sensation Seeking scales) compared to controls and nicotine users, but there was still a significant positive relationship between impulsivity and severity of cannabis use symptoms (Beaton et al., 2014). Similarly, when currently cannabis dependent individuals were compared to former users and controls there were no significant group differences on the BIS survey, and only currently cannabis dependent individuals score higher on the EIS (Johnson et al., 2010). In an inpatient sample, relationships were mostly absent between severity of cannabis dependence and personality domains within the UPPS-P (Moraleda-Barreno et al., 2018). Importantly, only 11% of this sample was receiving treatment for CUD and 73% of the respondents used cannabis only secondarily to their drug of choice most likely masking any cannabis-dependent effects. Altogether, these data may indicate there is not a unified impulsivity phenotype in cannabis users.

5.1.2 Moderators of trait impulsivity and cannabinoid use—Specific psychological factors have been shown to mediate some of the relationship between an impulsive personality and cannabis use outcomes. The acquired preparedness model, originally formulated based on alcoholism, theorizes that impulsivity influences outcome expectancies that regulate participation in risky behavior (McCarthy et al., 2001). Consistent with this model, expectancies about cannabis use mediate the link between impulsivity and cannabis use outcomes. Individuals high on trait impulsivity have more positive expectations for cannabis use, which in turn leads to higher cannabis use (Bolles et al., 2014, Buckner, 2013, Curry et al., 2018, Hayaki et al., 2011, Luba et al., 2018) and more cannabis related problems (Buckner, 2013, Curry, Trim, 2018). Specifically, the link between cannabis use and sensation seeking and cannabis use and positive urgency in the UPPS-P is mediated by expectancy (Curry, Trim, 2018, Luba, Earleywine, 2018). Negative expectancies can also mediate the relationship between trait impulsivity and use, although the nature of this relationship may be less straightforward. Negative cannabis expectancies were negatively correlated with cannabis use frequency and use onset (Buckner, 2013, Hayaki, Herman, 2011, Montes et al., 2019, Vangsness et al., 2005). In at least one study, negative expectancies still positively predicted severity of cannabis problems and cannabis dependence (Hayaki, Herman, 2011). Additionally, cannabis-related perceptions among college students (e.g., internalization of college cannabis use culture and injunctive norms) have been shown to mediate the effects of trait impulsivity and sensation seeking on frequency of cannabis use and cannabis-related problems (Pearson, Hustad, 2018). Similarly, sensation seeking is a moderator of social influence variables like peer pressure and peer use on cannabis consumption in middle school students (Slater, 2003).

5.1.3 Behavioral impulsivity and cannabinoid use—

The picture is less clear when it comes to behavioral impulsivity. In young adult cannabis users, poorer IGT performance was associated with more DSM-IV CUD symptoms (Gonzalez et al., 2012). In middle and high school students, greater discounting in a real-world delay of gratification paradigm was associated with higher frequency of cannabis use (Wulfert et al., 2002). Similarly, greater delay discounting was associated with earlier age of first cannabis use in college students (Kollins, 2003) and higher frequency of use in a large adult sample (ages 18–79) (Sofis, Budney, 2020). Yet often when cannabis users and cannabis dependent individuals have been compared to controls across decision making and behavioral inhibition tasks (DD of hypothetical monetary rewards, IGT, GNG, and SST) no significant differences have emerged (Delibaş, Akseki, 2018, Johnson, Bickel, 2010, Mejía-Cruz, Green, 2016, Quednow et al., 2007, Smith et al., 2014) but see (Moreno et al., 2012, Whitlow et al., 2004). Interestingly, cannabis dependent individuals discount delayed monetary losses, but not gains, more steeply than controls (Mejía-Cruz, Green, 2016). The implications of this finding are not completely clear, although this strategy of disadvantageous decision making could reflect the tendency of an individual to ignore future negative consequences of their actions which is a hallmark of addiction. Nevertheless in regular cannabis users steeper delay discounting of rewards is associated with cannabis problems and dependence (Aston et al., 2016, Heinz et al., 2013, Lopez-Vergara, Jackson, 2019, Strickland et al., 2017). Moreover, cannabis dependent individuals appear to discount cannabis more significantly than money or other commodities like leisure activities (Johnson, Bickel, 2010, Mejía-Cruz, Green, 2016). In a hypothetical cannabis purchase task, cannabis demand was also related to frequency of cannabis use (Aston, Metrik, 2016, Strickland, Lile, 2017). Overall, the evidence supports some association between impulsive behavior and cannabis use. The large variability in results across studies likely reflects significant differences in study design capturing both more acute and chronic effects, assessing recreational and pathological use, and likely captures both causative and drug-induced behavior.

5.2 Acute effects of cannabis on impulsivity

The acute effects of cannabis and its constituents on impulsivity have been directly studied in the human laboratory. One advantage of this strategy is that conditions like drug dose and timing can be strictly managed in placebo-controlled experiments. In recreational cannabis users, dose-dependent effects of orally administered THC capsules were examined in a battery of impulsivity-related behavioral tasks (SST, GNG, DD and a time reproduction task) (McDonald, 2003). THC was without effect on GNG or DD performance, but dose-dependently increased stop-reaction time in the SST (McDonald, 2003). Similar modest deficits on inhibitory control in the SST were obtained when subjects were provided high potency cannabis cigarettes (13% THC) (Ramaekers et al., 2006). In another unique study, both the pharmacological and expectancy effects of cannabis with low concentrations of THC were examined utilizing a two × two [(placebo or 2.8% THC) × (told placebo or told THC)] randomized factorial design (Metrik et al., 2012). At this relatively low concentration of THC (>2.5–5X lower than the aforementioned studies) cannabis modestly increased impulsivity on the SST and the Stroop task but did not alter experiential discounting or DD. Interestingly, the expectation of receiving THC may have produced compensatory effects on risky decision making in the experiential discounting task. In other words, when cannabis

was expected, whether or not it was received, the subject made more cautious decisions in an effort to mitigate the drug's anticipated effects. This effect has likewise been observed for risk-taking in the Balloon Analog Risk Task (BART) (Gunn et al., 2017). Acute THC or cannabis also has impairing effects on internal timing mechanisms (McDonald, 2003, O'Leary et al., 2003, Paasche et al., 2019). Although not directly a measure of impulsivity, time perception is obviously involved in impulsivity-related decision making.

Technological advancements including ecological momentary assessment have recently been utilized to assess acute cannabis effects in real world settings. During a two-week study in recreational drug users, cannabis use was associated with higher same-day and next-day impulsivity as measured using a daily within-subjects BIS-Brief survey (Ansell et al, 2015). In a similar study performed in a psychiatric outpatient population, cannabis use was associated with increased impulsivity only at the same day level on a momentary impulsivity scale (Trull et al., 2016). The dissimilarity in the effect on next-day impulsivity between these two studies could be attributed to the different self-report measures or the distinct subject pools. Interestingly, in both reports there was a lack of significant between-subjects association with level of cannabis use and impulsivity. This result might lend support towards a consequential more than causal model or could reflect limits associated with the sample demographics consisting of only recreational, non-dependent cannabis users. Future research should examine a wider variety of cannabis users. There may also be the potential to "gamify" this research and create platforms that integrate impulsivity surveys and modified computerized task-based measures to expand our understanding of acute and chronic cannabis effects.

5.3 Cannabis on the brain: pre-existing variations and post-drug use adaptations in neuroanatomy

Cheetham and colleagues were the first to provide support for a neural signature that predicts later cannabis use. In this important study, researchers found that smaller OFC volume at age 12 predicted initiation of cannabis use at 4-year follow-up (Cheetham et al., 2012). This finding was partially replicated in a longitudinal analysis that collected 3 waves of neuroimaging data along with comprehensive substance use assessments in a cohort of subjects oversampled for depression symptoms. Here OFC volume and thickness again measured at age 12 similarly negatively predicted subsequent onset and frequency of alcohol and cannabis use (Luby et al., 2018). A third study implicating the OFC in cannabis use vulnerability reported the inverse relationship. Larger left lateral OFC volume at baseline (age 12–15 years) predicted transition to regular cannabis use (Wade et al., 2019). Notably, a similar positive relationship between OFC volume and onset of cannabis use emerged in the Luby et al study when alcohol and cannabis use were separated (Luby, Agrawal, 2018). The Wade study differed from those preceding it in that the baseline measures were collected from subjects across a wider age range thus capturing greater heterogeneity in the neurodevelopmental snapshot. In addition, a larger proportion of the sample transitioned to substance use. This combination of factors may have contributed to the disagreement between results. Still other studies have failed to find any baseline differences in OFC volume, thickness, or surface area between future cannabis users and controls (Infante et al., 2018, Orr et al., 2019). The PFC is normally subject to extensive synaptic pruning and

refinement during adolescence, and the dynamic nature of individual variability in this maturational process could obscure some baseline differences. Additional longitudinal studies are essential to resolve the role of the OFC as a potential biomarker of susceptibility for CUD.

Cross-sectional studies about the effects of cannabis on the brain deliver mixed results. A variety of factors, including diverse subjects with variable patterns of use (infrequent vs. heavy), ages (adolescent vs. adults), poly-drug use, length of abstinence, and psychiatric comorbidity, may contribute to this variability. Analyses seem to indicate that even very low levels of cannabis use are capable of producing structural rearrangement. Whole brain gray matter volume was increased after as few as 1–2 uses of cannabis, prompting the authors to conclude that gray matter volume increases are drug-induced and not pre-existing (Orr, Spechler, 2019). Other studies lend additional support to a vulnerability model or at least suggest interactive mechanisms. A longitudinal and cross-sectional study examining cortical thickness before and after initiation of alcohol or cannabis+alcohol found modest baseline differences mostly in line with reduced cortical thickness in future cannabis+alcohol initiates. The primary finding was significant Group X Time interactions (control vs. alcohol initiators vs. cannabis+alcohol initiators comparing age 13 to age 19) emerging such that cannabis+alcohol users demonstrated a smaller decline in cortical thickness over time (Jacobus et al., 2016). Their findings indicated that cannabis use may disrupt the trajectory of cortical pruning but also hinted that pre-existing differences might contribute to cannabis initiation. The disruption in synaptic refinement may lead to the eventual increased cortical thickness in cannabis users compared to controls reported in some (Filbey et al., 2015, Jacobus et al., 2015) but not all (Scott et al., 2019) studies of adolescent users. Certainly, location matters because both increases and decreases in thickness were observed in separate brain regions of the same adolescent users (Lopez-Larson et al., 2011). The relationship between cannabis use and brain structure is complex, and gray matter volume analysis underscores the distinction between non-dependent versus dependent or occasional versus frequent use. Smaller OFC volume was associated with cannabis dependence and higher past month usage with a suggestion of differential sensitivity in female users compared to their male counterparts (Chye et al., 2017). Cannabis use, dependence, and related problems show consistent negative correlations with gray matter volume measurements of ROIs in the hippocampus, amygdala, and superior temporal gyrus (Cousijn et al., 2012, Koenders et al., 2016). Speaking to a progression of cannabis use effects, a decrease in gray matter volume in multiple regions (OFC, left insula, parahippocampal gyrus, temporal pole, and temporal cortex) was apparent in frequent cannabis users compared to occasional ones with comparable years of experience (Battistella et al., 2014); but in one longitudinal study ongoing use did not suggest continuing decline, although the “heavy” users in this study would likely qualify as intermediate to the occasional and frequent users in the aforementioned investigation (Koenders, Cousijn, 2016). Undoubtedly, age of use onset and other demographic and drug use factors additionally play a role in the outcome (Battistella, Fornari, 2014, Filbey, McQueeny, 2015).

Functional connectivity also shows evidence of alteration by cannabis use. Increased functional connectivity between OFC and frontal and motor cortical regions was observed in adolescent heavy cannabis users compared to controls (Lopez-Larson et al., 2015). In a

longitudinal study, lower basal connectivity between ACC and OFC predicted higher cannabis use at 18-month follow-up in a cohort of treatment seeking adolescents. Additionally, differential time-dependent alterations in functional connectivity distinguished cannabis users from controls. Healthy controls showed significant increases in connectivity between ACC and superior frontal gyrus, a trend absent in cannabis users; conversely, cannabis users, but not controls, displayed decreased connectivity between ACC and dlPFC (Camchong et al., 2017). Similar functional reorganization was observed in non-treatment seeking adolescent cannabis users (Camchong et al., 2019). Multi-voxel pattern analysis using rs-fMRI was used to identify a number of brain regions from PFC to cerebellum with distinct patterns of activity in adult male cannabis users compared to controls generating a RSFC signature that could classify cannabis users from controls with >84% accuracy (Cheng et al., 2014). Related to connectivity, alterations in white matter integrity primarily captured by fractional anisotropy measurements derived from diffusion tensor imaging have also been reported in association with cannabis use. Recent longitudinal analyses seem to support the notion that fractional anisotropy is reduced by cannabis, although perhaps in a restricted pattern, and the effects on white matter integrity are cumulative (Becker et al., 2015, Jakabek et al., 2016).

Some studies have examined differences in neural activation between cannabis users and controls associated with performance on impulsivity-related tasks. A recent comprehensive meta-analysis of neuroimaging studies described the brain regions that reliably demonstrate functional adaptations in cannabis users versus controls overlaying task-based network analysis to categorize the disrupted cognitive processes (Yanes et al., 2018). While a minority of the reviewed studies incorporated tasks related to response inhibition and impulsivity, their overall analysis identified three networks associated with cognitive control, attention, and reward linked to decreased activation in the ACC and dlPFC and increased activation in the striatum, respectively. Similarly, the OFC, ACC, and dlPFC emerged as common results in another meta-analysis directly focused on impulsivity (Wrege et al., 2014). In heavy cannabis users not (yet) showing deficits in IGT performance, significant alterations in task-related brain activation patterns were observed compared to controls (Acheson et al., 2015, Cousijn et al., 2013). Cannabis users showed higher responses to both Wins (Acheson, Ray, 2015, Cousijn, Wiers, 2013) and Losses (Acheson, Ray, 2015) in overlapping but non-identical clusters of brain regions compared to controls. Moreover, higher activity related to Win-Loss evaluation or disadvantageous vs. advantageous decisions predicted increased cannabis use at 6-month follow-up (Cousijn, Wiers, 2013). Relatedly, frequent cannabis users, though displaying equivalent accuracy on a GNG task, demonstrated impaired error awareness associated with hypoactivity of ACC, right insula and middle frontal regions (Hester et al., 2009), or slower reaction times on Go trials associated with a reduction in the P3 component of event related potential (Maij et al., 2017).

Finally, some enduring effects on neural function are observed in abstinent cannabis users. Persistent dose-related deficits in IGT were reported with heavy users showing worse performance associated with decreased activity in right lateral OFC and dlPFC compared to controls after 25 days of abstinence (Bolla et al., 2005). The users also displayed a flat learning curve across within-session trial blocks although there was significant learning

between sessions (Verdejo-Garcia, Benbrook, 2007). As reviewed in Section 5.2, in many instances cannabis users and former cannabis users do not differ behaviorally from controls, but adaptations can still be observed at the brain level suggesting functional compensation required to maintain equivalent performance. In 28-day abstinent adolescent cannabis users, neural responses were increased during both Go and No Go trials in a GNG task (Tapert et al., 2007). Cannabis users displayed greater blood oxygen-level dependent signal responses during inhibition trials in an expected pattern including dlPFC, bilateral medial frontal, bilateral inferior and superior parietal lobes, and right occipital gyrus (Tapert, Schweinsburg, 2007). Similarly, in a Decision-Reward Uncertainty Task adolescent former cannabis users showing unchanged behavior exhibited hyperactivation in left superior parietal, left lateral occipital, and precuneus while making risky decisions involving uncertainty and hypoactivation in left OFC to rewarded outcomes after making risky decisions (De Bellis et al., 2013).

5.4 Cannabis on the brain: cannabis use effects on neurotransmission

The THC in cannabis produces its effects by acting on the endocannabinoid system inclusive of endogenous cannabinoids, their receptors, and biosynthetic and degradative enzymes. The two primary endocannabinoids arachidonyl ethanolamide (anandamide) and 2-arachidonylglycerol are synthesized and degraded by separate enzymatic pathways that contribute to their distinct functions (Lu and Mackie, 2016). Unlike standard neurotransmitters, endocannabinoids are produced in an activity dependent fashion by the postsynaptic neuron and function in a retrograde manner to stimulate presynaptic cannabinoid receptors. The CB_1 receptor is the primary central nervous system subtype, and in fact, represents one of the most highly expressed G-protein coupled receptors in the brain (Busquets-Garcia et al., 2018). Cannabinoid receptors preferentially couple to $G_{i/o}$ signaling proteins exerting their effects through inhibition of adenylyl cyclase or facilitation of K^+ channel conductance resulting in hyperpolarization and inhibition of neurotransmitter release (Gardner, 2005). Most of the effects of THC, including reward, are blocked with a CB_1R antagonist (Pertwee, 2008). Not surprisingly, CB_1 receptor density is high in many of the same brain regions that show neuroanatomical alterations following cannabis use (Lorenzetti et al., 2016). Positron emission tomography (PET) scans showed that CB_1 receptor binding was decreased broadly across cortical regions in cannabis users and negatively correlated with years of use, although this deficit normalized within a month of abstinence (Hirvonen et al., 2012).

Cannabis or THC, akin to other addictive drugs, increases dopamine release in the striatum (Bossong et al., 2015, Cadoni et al., 2008, Chen et al., 1990, Voruganti et al., 2001). The acute activation of CB_1 receptors on inhibitory GABAergic terminals apposed to ventral tegmental area dopamine neurons reduces GABA release with a net effect of increasing dopamine neuron firing and downstream dopamine signaling (Covey et al., 2017). Impulse control and reward are both linked to dopamine transmission, and the endocannabinoid system might be one bridge that links the two. Chronic cannabis use reduced dopamine synthesis, an effect positively related to the severity of use (Bloomfield et al., 2014). Cannabis and tobacco smokers showed reduced DAT availability in the striatum (Leroy et al., 2012). Thus, chronic cannabis use reduces dopaminergic function. At least one study

demonstrated that polymorphisms in the dopamine-beta-hydroxylase enzyme (CT/TT vs CC genotypes), expected to influence tonic dopamine levels, altered behavioral and biological response to acute cannabis challenge in current drug users (Ramaekers et al., 2016). Only individuals with the low activity CT/TT genotype displayed increased cognitive impulsivity in the Matching Familiar Figures Test (Ramaekers, van Wel, 2016). There is little direct evidence of cannabis' effects on 5-HT neurotransmission in humans, but preclinical *in vitro* and *in vivo* studies indicate that cannabidiol, a major non-intoxicating chemical component of cannabis, is an agonist at 5-HT receptors (De Gregorio et al., 2019, Russo et al., 2005). Several recent genetic studies point to interactions between the 5-HT system and cannabis use or cannabis use outcomes (Galindo et al., 2018, Verdejo-García et al., 2013). Researchers recently identified functional_CB_1- 5- HT_{2A} receptor heteromers in the olfactory neuroepithelium of control subjects that were increased in cannabis users (Galindo, Moreno, 2018). Moreover, in cannabis users these heteromers positively correlated with amount of cannabis use and negatively correlated with age of use onset and cognitive performance (Galindo, Moreno, 2018). All of the evidence regarding the effect of cannabinoids on noradrenergic signaling has been gleaned from animal studies. Acute THC increased locus coeruleus neuron activity (Muntoni et al., 2006). Interestingly, this was likely an indirect effect not involving local CB1 receptors given that intracereberoventricular delivery of cannabinoid agonists failed to increase locus coeruleus firing rate (Mendiguren and Pineda, 2006). The effects of chronic cannabinoid use on noradrenergic signaling remain unknown. Atomoxetine has been tested for efficacy in treating cannabis use disorder, and it failed to reduce drug craving or use (McRae-Clark et al., 2010).

CB_1 receptors are expressed on presynaptic terminals of glutamatergic and GABAergic synapses throughout the brain (Busquets-Garcia, Bains, 2018). Preclinical studies show that acute THC disrupts glutamate signaling but the nature of that effect is varied. THC reduced glutamate release in the striatum (Orrú et al., 2011, Sano et al., 2008) but increased extracellular glutamate levels in the PFC (Pistis et al., 2002). In healthy control human subjects with moderate former cannabis use, acute THC increased levels of glutamate plus glutamine metabolites (Glx) in the left caudate nucleus (Colizzi et al., 2019). Interestingly, the psychotomimetic effects of cannabis were most prominent in those individuals with the greatest fold change in Glx levels (Colizzi, Weltens, 2019). Similarly, in occasional cannabis users acute THC increased glutamate concentrations in the right striatum (Mason et al., 2019). These results are interesting in light of the fact that chronic cannabis users consistently display reduced glutamate levels (Chang et al., 2006, Muetzel et al., 2013, Prescot et al., 2013) but see (Blest-Hopley et al., 2019). Basal glutamatergic deficits would be consistent with the glutamate homeostasis hypothesis of addiction with augmented glutamate overflow in response to a cannabis challenge predicted to exacerbate relapse (Scofield et al., 2016). In another recent examination of neurometabolite concentrations in the dorsal ACC where the authors did not detect a decrease in glutamate concentration in chronic cannabis users compared to controls, total creatine was positively associated with monthly cannabis use; therefore, the authors appropriately did not normalize to this measure (Newman et al., 2019). This particular finding may have implications for the interpretation of previous results and should inform the design and analysis of future studies. Reduced GABA concentrations in dorsal ACC paralleled the lower glutamate levels in adolescent

chronic cannabis users (Prescot, Renshaw, 2013). Likewise, in a rat microdialysis assay THC decreased extracellular GABA levels in the PFC (Pistis, Ferraro, 2002). Another preclinical study found that repeated THC exposure during adolescence reduced GAD_{67} levels and GABA concentration in the adult PFC (Zamberletti et al., 2014). These findings were replicated and extended to demonstrate a connection between cortical GABAergic hypo-function and VTA dopamine hyper-function (Renard et al., 2017). Such a result might go towards explaining poorer cannabis and other substance use outcomes associated with earlier age of use onset (Rioux et al., 2018).

6. Conclusions

Trait impulsivity has predictive value for cannabis use outcomes. Trait impulsivity may influence some of the subjective effects of acute cannabis (Van Wel, 2015). This is important because subjective effects in response to cannabis have noted association with use patterns and dependence (Zeiger et al., 2010). The same might be true for behavioral impulsivity, but there is currently a lack of longitudinal data to fully support that notion. In cross-sectional studies, cannabis users/individuals with CUD do not reliably display increased trait or behavioral impulsivity compared to controls. Instead, elevated impulsivity in either of these domains is often related to age of use onset, frequency of use, and other negative outcomes/problems. Acute effects of cannabis do increase state impulsivity. Impulsivity also moderates other factors contributing to cannabis use like individual expectancies or social influences. Here we examined both impulsivity and sensation seeking based on the idea that "impulsivity" is not a single construct. Sensation seeking, like impulsivity, showed prospective associations with cannabis use. It has actually been suggested that sensation seeking may be more tied to onset of substance use while impulsivity is related to continued use and associated problems. In line with that model, the TRacking Adolescents' Individual Lives Survey found that higher BAS function increased the likelihood of ever using cannabis while lower BIS function promoted repeated cannabis use (van Leeuwen et al., 2011). Early sensation seeking interventions may be beneficial to certain high-risk populations (Mahu et al., 2015).

There is significant neuroanatomical overlap between the brain regions implicated in impulsivity and those affected by cannabis use. In particular, the OFC stands out with a high density of CB_1 receptors. The precise role of the OFC in decision-making and impulsivity remains under investigation somewhat complicated by the functional heterogeneity of this region's medial and lateral subdivisions including a dissociation between impulsive choice and impulsive action (Mar, Walker, 2011, Ucha et al., 2019). A positive relationship between *CNR1* gene expression in medial OFC and impulsive choice has been described in rodents (Ucha, Roura-Martínez, 2019). Differential OFC activation patterns were associated with delayed versus immediate rewards in human imaging studies (McClure, Laibson, 2004). CB_1 receptors regulate sensitivity to the effects of cannabis, but to our knowledge there is currently no longitudinal evidence indicating that baseline CB_1 receptor levels in the OFC or elsewhere predict cannabis use or CUD outcomes. With the relatively recent development of radioligands for PET imaging, these studies may be yet on the horizon (Burns et al., 2007). Until then, there is already evidence of a predictive relationship between OFC volume and cannabis use, although it is perhaps still up for debate whether a smaller or larger OFC

confers this vulnerability (Cheetham, Allen, 2012, Wade, Bagot, 2019). Less controversial is the evidence that chronic, heavy cannabis use has widespread neurotoxic effects resulting in losses in gray matter volume (Battistella, Fornari, 2014, Chye, Solowij, 2017). In contrast, another consistent finding was increased gray matter volume in the cerebellum (Battistella, 2014, Cousijn, 2012, Koenders, 2016), but the functional significance of this adaptation remains uncertain. Additional unbiased analysis methods and larger sample sizes will provide further refinement of the altered brain map that is developing.

There are similar neurochemical signatures associated with impulsivity and cannabis use. The catecholamine neurotransmitters 5-HT and dopamine are most commonly associated with trait impulsivity and impulsivity-related behavior (Pattij and Vanderschuren, 2008). Cannabis, like all abused drugs, acutely stimulates dopamine release in the ventral striatum (Bossong, Mehta, 2015); however, a hypodopaminergic state develops with chronic cannabis use (Bloomfield, Morgan, 2014). Interestingly, this dopaminergic hypofunction does not extend to lower baseline D2/D3 receptor availability in the striatum of cannabis users compared to controls (Volkow et al., 2014), an effect observed seemingly ubiquitously across other abused drugs and often (but not always (Castrellon, Seaman, 2019)) associated with impulsivity (Trifilieff and Martinez, 2014). As with the neuroanatomical brain imaging data, it would be beneficial to track neurochemical changes across time with cannabis use to explore possible explanations for this seeming incongruency. Likewise, while the behavioral pharmacology linking 5-HT and norepinephrine to impulsivity is strong (Pattij and Vanderschuren, 2008), there is a substantial gap in our knowledge concerning the direct effects of cannabis use on the serotonergic and noradrenergic systems. Perhaps this is partially explained due to the fact that the CB_1 receptor mediated modulation of their activity occurs indirectly via primary actions at glutamatergic and GABAergic terminals (Mendiguren and Pineda, 2006). It is thus not surprising that there is substantial evidence that cannabis use disrupts glutamate and GABA transmission, though the direction of effects may not always be consistent. Given the substantial baseline impulsivity dependent effects that have been described elsewhere (Herman, Critchley, 2019), it would not be implausible to hypothesize that such state dependence may also be observed for effects of cannabis use on neurotransmission.

In the previous sections we have tried to summarize the evidence for a bidirectional relationship between impulsivity and cannabis use. Collectively, these data provide support for several hypotheses. 1) It is possible that very similar pre-existing differences in the brain underlie impulsivity and confer vulnerability to CUD. 2) An alternative explanation provides for a more linear sequence of events. For example, PFC-related or other impairments may promote trait impulsivity, and that elevated impulsive phenotype then mediates cannabis use outcomes. Similarly, the inverse relationship is conceivable with some biological endophenotype conferring risk for cannabis use, and that cannabis use increases behavioral impulsivity. 3) A third likely scenario that we have not spent much time elaborating on here is that the developing adolescent brain is particularly sensitive to the effects of drugs, including cannabis, which interrupt normal maturational processes. From the rodent literature, chronic agonism of the CB_1 receptor during adolescence but not adulthood, promotes elevated impulsivity in a DD task later in adulthood (Johnson et al., 2019). The fact that age of use initiation affects brain changes and use outcomes in humans lends

support to this non-mutually exclusive theory (Filbey, McQueeny, 2015, Gruber et al., 2014). At this point, there is seemingly evidence to support any of these ideas. Cannabis users and individuals with CUD are highly heterogeneous; therefore, it is likely that the true answer is "all of the above" with different trajectories observed in distinct populations interacting with other risk factors (family history, genetics, environmental influences). We have provided the relevant longitudinal data where it exists. Additional prospective studies are necessary to begin to parse out these causes and effects. Impulsivity and cannabis use have a biological basis and are moderately heritable (Bezdjian et al., 2011, Verweij et al., 2010), but researchers are still connecting the dots between the two.

7. Future directions

In brief, we highlight here a few additional related areas for future research. First, there is burgeoning data related to epigenetic mechanisms and transgenerational transmission associated with cannabis use (Szutorisz and Hurd, 2018). Epigenetic modifications brought about by cannabis use can contribute to enduring changes in gene expression and behavior. Few studies have specifically examined the transgenerational relationship between cannabis use and impulsivity, but available studies argue for both direct and indirect effects of parental cannabis use on their progeny's outcomes (Fried and Smith, 2001, Goldschmidt et al., 2000, Oshri et al., 2018, Riggs et al., 2009). With US trends of increasing cannabis use, including among pregnant mothers (SAMHSA, 2019, Volkow et al., 2019), there is a need for more research in this realm incorporating genomic analysis to complement behavioral and personality assessments.

Pharmacological interventions targeting impulsivity may be particularly effective for a subset of patients seeking CUD treatment. It has already been demonstrated that high impulsivity may portend worse treatment responses for individuals with SUDs (Loree, Lundahl, 2015), suggesting patients with specific disease etiology related to that dysfunction may benefit from individualized interventions. Currently, there are no approved pharmacotherapies for CUD, but many treatments are under investigation. Although data is not conclusive, there is limited evidence that pharmacotherapies such as n-acetylcysteine and citicoline may affect impulsivity (Bentzley, Tomko, 2016, Gruber et al., 2015, Licata et al., 2011, McGlade et al., 2019) and continued investigation of these drugs as adjunctive therapies combined with other approaches (e.g., cognitive behavioral therapy or neuromodulation) is recommended. Neuromodulation in healthy controls can modulate impulsivity, but this parameter has not been assessed in cannabis users (Yang et al., 2018). There is still much to be learned about the mechanisms of neuromodulation and how to optimize and individualize parameters, but there is already a lot of optimism around adopting non-invasive circuit based interventions for the treatment of SUDs (Spagnolo and Goldman, 2017).

In conclusion, there is good scientific evidence supporting an association between impulsivity and cannabis use. Cumulative data support a role for impulsivity as a risk factor for, and consequence of, cannabis misuse. Some of the variability in the literature likely stems from the fact that both impulsivity and CUDs represent dimensional behaviors. Complicating matters further is the fact that trait and state impulsivity are not well

correlated, nor is the distinction between impulsivity and sensation seeking always well defined. Similarly, the etiology of CUD is multifactorial. Available data strongly support a predictive relationship between trait impulsivity and cannabis use parameters; still, prospective studies remain few and far between and this model would be bolstered by additional longitudinal data including into transgenerational effects. Conversely, current cannabis use is associated with surprisingly modest effects on behavioral impulsivity despite significant evidence of neurobiological adaptations in relevant brain circuits. Additional research that takes into account important moderating factors including age of use onset interactions, functional compensation, and abstinence-induced recovery will be important for clarifying this relationship. Studies examining the long-term trajectories of CUD will be helpful for designing more evidence-based strategies for treating the individual etiologies of this complex disorder. Targeting the neurobiological component of impulsivity may be just one piece of a multi-pronged approach for treating CUD.

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Abbreviations

#CSRTT	1–5-choice serial reaction time task
5-HT	5-hydroxytryptamine
ACC	anterior cingulate cortex
ADHD	attention-deficit/hyperactivity disorder
BART	balloon analog risk task
BIS	Barratt Impulsiveness Scale
BIS/BAS	Behavioral inhibition system/Behavioral approach system
BSSS	Brief Sensation Seeking Scale
CB_1	cannabinoid 1 receptor
CNR1	cannabinoid receptor 1 gene
CPT	continuous performance task
CUD	cannabis use disorder
DAT	dopamine transporter
DD	delay discounting task
dlPFC	dorsolateral PFC
DREADDs	designer receptors exclusively activated by designer drugs
DSM	diagnostic and statistical manual of mental disorders

EIS	Eysenck Impulsiveness Scale
fMRI	functional magnetic resonance imaging
GABA	gamma-aminobutyric acid
GAD	glutamate decarboxylase
GNG	go/no go task
IGT	Iowa gambling task
NAc	nucleus accumbens
NMDA	N-methyl-d-apartate
OFC	orbitofrontal cortex
PET	positron emission tomography
PFC	prefrontal cortex
rGT	rat gambling task
ROI	region of interest
RSFC	resting state functional connectivity
rs-fMRI	resting state fMRI
SSS	sensation seeking scale
SST	stop-signal task
SUD	substance use disorder
SURPS	substance use risk profile scale
THC	delta9-tetrahyrdocannabinol
UPPS-P	negative Urgency, (lack of) Premeditation, (lack of) Perseverance, Sensation seeking, Positive urgency
VTA	ventral tegmental area

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Highlights

- Both impulsivity and cannabis use disorder represent dimensional behaviors.
- Trait impulsivity is consistently implicated as a risk factor for both cannabis use and cannabis-related problems.
- The neural networks and neurochemical substrates that underlie impulsivity share significant overlap with the neurobiological disruptions produced by chronic cannabis use.
- Impulsivity may precede cannabis use or manifest as a function of chronic cannabis experience.

Box 1:

DSM IV vs. DSM-5 for cannabis use disorder

The diagnostic and statistical manual of mental disorders (DSM) is the handbook published by the American Psychiatric Association used by healthcare professionals in the US to aid in the diagnosis of psychiatric conditions. First published in 1952, the DSM contains symptoms and other descriptive criteria for making reliable and consistent diagnoses. It is periodically updated to reflect the most up-to-date research and clinical evidence. The current version is the DSM-5, which was released in 2013. Consequently, much of the human subjects research cited in this review was conducted under DSM-IV criteria even though some of it has been published since the DSM-5 transition. Accordingly, it is pertinent for our interpretation of the following findings to understand the impact of this change. The DSM-5 merged the DSM-IV subcategories of abuse and dependence and added cannabis withdrawal and craving as criterions of CUD to reflect substantial research documenting their clinical importance (Hasin et al., 2013, Katz et al., 2014). DSM-5 also dropped cannabis-related legal problems as a criterion (Hasin, O'Brien, 2013). DSM-IV assessed cannabis abuse and cannabis dependence as separate constructs without recognizing cannabis withdrawal or craving (APA, 1994). A diagnosis of cannabis abuse required meeting at least 1 of 4 criteria. A diagnosis of cannabis dependence required meeting at least 3 of 6 criteria. Notably, hierarchical diagnostic rules placed more emphasis on a diagnosis of dependence such that individuals ever meeting criteria for dependence were excluded from receiving a diagnosis of abuse for the same substance. In practical terms, cannabis dependence was considered the more severe disorder. In line with the DSM-5 changes, research suggests that endorsement of cannabis abuse items can indicate just as serious substance use problems (Hartman et al., 2008).

Following the release of the DMS-5, Hasin and colleagues analyzed findings from the 2012–2013 National Epidemiologic Survey on Alcohol and Related Conditions using both DSM-IV and DSM-5 evaluative criteria. Under DSM-IV criteria, 2.9% of those surveyed could be diagnosed with CUD (Hasin et al., 2015). Under updated DSM-5 criteria, the prevalence of past year CUD was 2.54% with a breakdown of 1.38%, 0.59% and 0.57% for mild, moderate and severe CUD, respectively (Hasin, 2016). Notably, there was relative congruence between the statistics derived from each set of diagnostic criteria.

Table 1.

Self-report impulsivity measures

Test name	Reference	Description
Barratt Impulsiveness Scale (BIS)	(Patton et al., 1995)	The BIS-11 is a 30 item questionnaire designed to assess impulsivity across three factors: attentional/cognitive, motor, and nonplanning.
Eysenck Impulsiveness Scale (EIS)	(Eysenck and Eysenck, 1978)	The EIS is a 63 item questionnaire that assesses personality traits of impulsivity, venturesomeness, and empathy.
Zuckerman's Sensations Seeking Scale (SSS)	(Zuckerman et al., 1964)	The SSS is a 40 item forced choice questionnaire consisting of four inter-related subscales: boredom susceptibility, disinhibition, experience seeking and thrill and adventure seeking.
Brief Sensation Seeking Scale (BSSS)	(Stephenson et al., 2003)	The BSSS is a condensed 8 item scale in Likert-type response format that maintains the four SSS subscales.
Behavioral Inhibition System/Behavioral Approach System (BIS/BAS)	(Carver and White, 1994)	The BIS/BAS is a 24 item questionnaire designed to measure the two motivational systems: the BIS which corresponds to motivation to avoid aversive outcomes and the BAS which corresponds to motivation to approach positive outcomes.
UPPS Scale	(Whiteside and Lynam, 2001)	The UPPS is a 45 item questionnaire designed to measure four personality traits associated with impulsivity: Negative Urgency, Lack of Premeditation, Lack of Perseverance, and Sensation Seeking.
UPPS-P Scale	(Cyders, Smith, 2007)	The UPPS-P is a 59 item questionnaire that adds the Positive Urgency scale to the UPPS.

Table 2.

Impulsivity behavioral tasks

Task Name	Reference	Description	Type
Impulsive Choice			
Go/No Go (GNG)	(Eagle and Baunez, 2010, Verbruggen and Logan, 2008)	Individuals are trained to perform an action in response to stimulus “A” (go) and withhold that action in response to stimulus “B” (no-go).	Stopping
Stop Signal Task (SST)	(Eagle and Baunez, 2010, Verbruggen and Logan, 2008)	Individuals are tasked with cancelling their already initiated action in response to a stop signal delivered at varying delays after a go signal.	Stopping
Continuous Performance Task (CPT)	(MacQueen et al., 2018a)	There are many variations that require individuals sustain focus and attention to a repetitive task in order to respond to targets or inhibit response to foils.	Waiting
#-Choice Serial Reacton Time Task (# = 1–5CSRTT)	(Robbins, 2002, Voon et al., 2014)	Originally developed as rat version of CPT. Subjects must pay attention to up to 5 locations and suppress responding until an unpredictable stimulus signals that it is appropriate to respond.	Waiting
Impulsive Action			
Delay Discounting (DD)	(Vanderveldt et al., 2016)	Individuals are required to choose between either small immediate or larger delayed rewards.	Temporal Delay
Probability Discounting	(Mejia-Cruz et al., 2016)	Individuals are required to choose between either small certain or larger uncertain rewards.	Uncertainty
Iowa Gambling Task (IGT)	(Verdejo-Garcia et al., 2007)	Individuals are instructed to maximize winnings while choosing repeatedly from four card decks that unpredictably yield wins and losses.	Uncertainty
Rat Gambling Task (rGT)	(Zeeb and Winstanley, 2011)	Variation on the IGT where rodent attempts to maximize rewards earned between four options that vary in reward magnitude on gain trials and time-out duration and probability of footshock punishment on loss trials.	Uncertainty