# Vulnerability of Compulsive Traits in Drug Addiction Behavior and Its Neural Basis in the Prefrontal-Anti-reward System

**Authors:** Yan Wansen, Liu Sujiao, Zhang Ranran, Xu Peng, Yan Wansen

**Date:** 2021-03-21T00:00:00+00:00

## Abstract

Compulsivity is a neuropsychological construct closely associated with perseverative behavior despite adverse consequences, and the collapse of neural regulatory mechanisms over compulsive behavior constitutes a direct cause of drug addiction. While previous research has accumulated rich understanding of the role and mechanisms of the reward system (mesocorticolimbic neural circuits) in addictive behavior, understanding remains limited regarding the compulsive features of drug addiction per se and the mechanisms of prefrontal-anti-reward neural circuits in addictive behavior, particularly lacking systematic investigation of compulsive features of drug addiction, genetic studies, and convergent evidence from non-stimulant drugs. This project proposes to integrate a genetic perspective on human addictive behavior (using heroin addicts and their drug-free siblings as controls), combining methods and techniques across neurocognitive, electrophysiological, and neuroimaging levels to explore the external manifestations, neurobiological underpinnings, and genetic susceptibility related to individual differences in drug addiction compulsivity, aiming to further identify neurobiological markers of drug addiction and provide additional evidence for exploring potential pharmacological or non-pharmacological intervention targets.

## Full Text

## Preamble

**Compulsivity and Its Susceptibility in Drug Addiction: The Neural Substrates of Prefrontal-Anti-reward System Mechanisms**

YAN Wan-Sen, LIU Su-Jiao, ZHANG Ran-Ran, XU Peng
(College of Medical Humanities, Guizhou Medical University, Guiyang 550025, China)

## Abstract

Compulsivity represents a neuropsychological construct closely associated with perseverative behaviors that persist despite severe negative consequences, and the breakdown of neural mechanisms governing compulsive behavior constitutes a direct cause of drug addiction. While previous research has yielded substantial insights into the role of the reward system (meso-cortico-limbic circuitry) in addictive behaviors, our understanding remains limited regarding compulsivity itself as a feature of drug addiction and the involvement of prefrontal-anti-reward system neural circuits, particularly lacking systematic investigation of compulsive traits in drug addiction, genetic studies, and convergent evidence from non-stimulant substances. This project aims to explore the phenotypic manifestations, neurobiological underpinnings, and genetic susceptibility related to individual differences in drug addiction compulsivity by integrating a genetic perspective on human addiction (comparing heroin addicts with their drug-free siblings) with multi-level methodologies spanning neurocognitive assessment, electrophysiology, and neuroimaging. We anticipate that this work will further identify neurobiological markers of drug addiction and provide additional evidence for potential pharmacological or non-pharmacological intervention targets.

**Keywords:** drug addiction, compulsivity, anti-reward system, prefrontal cortex, limbic system

## 1. Research Background and Significance

Drug addiction is a chronic, relapsing brain disease characterized primarily by compulsive drug-seeking and drug-taking behaviors with loss of control over consumption (Goldstein & Volkow, 2002; Leshner, 1997). Once severe addiction develops, no definitive treatments currently exist except for certain substitution therapies. Therefore, identifying neurobiological markers associated with addiction vulnerability and developing targeted interventions represent critical scientific missions in addiction research. Compulsivity is a neuropsychological construct intimately linked to perseverative actions despite adverse consequences and constitutes a core feature of drug addiction (Dalley et al., 2011; Lüscher et al., 2020; Robbins et al., 2012). Multiple diagnostic criteria for drug addiction relate directly to compulsivity, including spending excessive time obtaining drugs, continued use despite serious social or interpersonal problems, and persistent use despite recurrent physical or psychological issues (American Psychiatric Association, 2013). Research indicates that approximately 20% of individuals using addictive substances (e.g., cocaine, heroin, amphetamines) ultimately develop compulsive drug use or addiction (Pascoli et al., 2018; Yücel et al., 2019), suggesting the existence of important individual susceptibility mechanisms underlying the transition to compulsive drug use (Agrawal et al., 2012; Everitt et al., 2008; Koob & Volkow, 2016).

Over recent decades, addiction research focusing on the mesolimbic dopamine

system has demonstrated that neurochemical alterations in brain reward circuits (e.g., ventral tegmental area, nucleus accumbens) and deficits in top-down inhibitory control from the prefrontal cortex play crucial roles in addiction development (Goldstein & Volkow, 2002, 2011; Koob, 2017; Koob & Le Moal, 2005). Consistent with this view, reward deficiency, sensation seeking, and impulsivity have been identified as potential vulnerability traits and genetic risk factors for drug addiction (Comings & Blum, 2000; Dalley et al., 2007; de Wit, 2009; Ersche et al., 2010, 2011, 2013; Verdejo-García et al., 2008; Volkow et al., 2002; Volkow & Morales, 2015; Luijten et al., 2017). These findings provide important explanations for drug use initiation, maintenance, and loss of control over craving and impulses. However, reward system-based theoretical frameworks and evidence remain insufficient to fully elucidate the highly complex processes and neurobiological mechanisms underlying drug addiction, particularly regarding compulsivity itself and its underlying mechanisms (Janak, 2018; Koob & Le Moal, 2005).

Generally, addiction emerges through a transition from casual drug use to habitual use and finally to compulsive use (Everitt et al., 2008). During this process, behavior patterns shift from reward-driven to habit-driven, with a corresponding neuroanatomical transition in the control of drug-seeking behavior from the ventral striatum/nucleus accumbens to the dorsal striatum (Everitt & Robbins, 2005, 2013, 2016; Gardner, 2011). From a neurobiological perspective, the breakdown of neural mechanisms that normally regulate habitual or more severe compulsive behaviors constitutes a direct cause of drug addiction. Therefore, in-depth exploration of genetic traits, neural structural and functional characteristics, and cellular-molecular mechanisms related to compulsivity provides a foundation for explaining core addiction mechanisms, identifying potential intervention targets, and developing targeted treatments (Koob, 2017).

The anti-reward system, proposed over the past decade, is considered to play a critical role in mediating compulsive drug use (Koob & Le Moal, 2005, 2008; Koob & Volkow, 2016; Koob, 2017). Unlike the reward system, which primarily regulates addiction through positive reinforcement, the anti-reward system governs mechanisms related to negative emotion, stress responses, conditioning, and habit-driven actions. Its primary neuroanatomical substrate is the extended amygdala, including the central nucleus of the amygdala, bed nucleus of the stria terminalis, and shell of the nucleus accumbens (Koob & Le Moal, 2005, 2008; Koob, 2013, 2017; Koob & Volkow, 2016; Volkow & Morales, 2015). These regions share similar morphological structures, neurotransmitter profiles, and neural projections, receiving substantial output from frontal cortical and limbic structures (e.g., basolateral amygdala, hippocampus) and projecting to the ventral pallidum and lateral hypothalamus, thereby connecting limbic emotional structures with the extrapyramidal motor system. These areas release neurotransmitters associated with negative emotional experiences and stress responses, including corticotropin-releasing factor, norepinephrine, and dynorphin. Following drug cessation or withdrawal, these neurochemicals are secreted in large quantities, producing dysphoria, anxiety, irritability, anhe-

donia, and enhanced stress reactivity, which drive individuals to compulsively seek and use drugs to alleviate these aversive states (Everitt & Robbins, 2016; Koob & Volkow, 2016; Volkow & Morales, 2015). Since drug reward effects are most prominent during initial use but diminish or disappear with continued use and developing tolerance (e.g., with opioids), the negative effects generated by the anti-reward system become the primary motivational driver maintaining compulsive drug use in later stages. Thus, compulsive mechanisms in drug addiction appear closely related to anti-reward system dysfunction. However, as a subcortical structure located in the basal forebrain, the anti-reward system not only has its own neurophysiological and neurochemical operations but also receives top-down control from the prefrontal cortex, forming an integral component of fronto-striatal circuits. For instance, circuits from the dorsolateral prefrontal cortex, inferior frontal gyrus, and lateral orbitofrontal cortex to the dorsal striatum (caudate, putamen) regulate behavioral inhibition, stereotyped actions, and compulsive behaviors, while circuits from the ventromedial prefrontal cortex and orbitofrontal cortex to the ventral striatum/nucleus accumbens, central amygdala, and bed nucleus of the stria terminalis regulate reward evaluation, positive and negative emotional motivation, aversive experiences, and stress responses (Ch' ng et al., 2018; Haber, 2003; Koob & Volkow, 2016; Krüger et al., 2015; Moorman, 2018; Robbins et al., 2012; Volkow & Morales, 2015). Therefore, compulsive features in drug addiction may arise through three pathways: (1) structural and functional dysregulation of the anti-reward system (hyperactive neurophysiological function); (2) impaired prefrontal control systems (weakened top-down inhibitory function); or (3) a combination of both. Most researchers currently favor the view that compulsivity in drug addiction results from the combination of hyperactive negative effects from the anti-reward system and functional impairments in prefrontal control systems (Koob, 2017; Koob & Volkow, 2016; Lüscher et al., 2020; Volkow & Morales, 2015).

Nevertheless, current understanding remains limited regarding the specific developmental processes, neurobiological substrates, and individual-difference-related genetic susceptibility underlying compulsive mechanisms in drug addiction (Janak, 2018; Koob & Le Moal, 2005; Volkow & Morales, 2015). Most studies have been restricted to animal models, neuropharmacology, and stimulant drugs, with scarce convergent evidence from human addiction research incorporating genetics, neurocognition, neuroimaging, and non-stimulant drugs (Just et al., 2019; Hynes et al., 2018; Koob & Volkow, 2016; Luikinga et al., 2018; Pascoli et al., 2018). In light of these gaps, this project proposes to investigate the genetic susceptibility and prefrontal-anti-reward system neural mechanisms of compulsivity in drug addiction, using human non-stimulant drug (heroin) addiction as a model. By integrating genetic methods (comparing addicts with their drug-free siblings), neurocognitive and neurophysiological approaches, and neuroimaging techniques, we aim to explore the neurobiological basis of compulsivity and its hereditary vulnerability, thereby providing empirical support for identifying key biomarkers of drug addiction.

## 2.1 Manifestations and Measurement of Compulsivity

Compulsivity is generally defined as "a tendency toward perseverative actions that are inappropriate to the situation and not clearly related to overall goals, often resulting in numerous unexpected negative consequences" (Dalley et al., 2011; Robbins et al., 2012). Individuals with compulsive traits often recognize the harmfulness of their behaviors yet remain driven by emotions to compulsively act in order to reduce tension, stress, or anxiety (Berlin & Hollander, 2014). The construct encompasses multiple psychological components, including cognitive and behavioral rigidity, inflexible strategies, attentional set-shifting deficits, impaired inhibitory control, reversal learning perseveration, resistance to change, and inappropriate persistence (Robbins et al., 2012). In animal models of compulsive behavior, researchers typically employ paradigms where animals (e.g., mice) continue seeking drug rewards (e.g., cocaine) despite physical punishment (e.g., foot shock) to simulate human compulsive drug-seeking and drug-taking behaviors (Deroche-Gamonet et al., 2004; Vanderschuren & Everitt, 2004). For human assessment, standardized measurement tools include the Yale-Brown Obsessive-Compulsive Scale (YBOCS; Goodman et al., 1989), the Obsessive Compulsive Drug Use Scale (OCDUS; Franken et al., 2002), and the Padua Inventory of Obsessive Compulsive Disorder Symptoms (PI-WSUR; Burns et al., 1996). While YBOCS is more suitable for obsessive-compulsive disorder patients, OCDUS specifically targets substance-using populations, and PI-WSUR is appropriate for general populations. At the neurocognitive level, compulsivity is thought to reflect deficits in top-down cognitive control or response inhibition mediated by the prefrontal cortex (Dalley et al., 2011; Koob & Volkow, 2016). Commonly used cognitive tasks include response inhibition tasks such as Go/No-Go, Stop Signal, and Stroop tasks (Logan et al., 1997; Macleod, 1991); set-shifting tasks like the Intradimensional/Extradimensional set-shifting task (IDED; Grant et al., 2010); and cognitive flexibility or reversal learning tasks such as the Wisconsin Card Sorting Task (WCST; Heaton & Staff, 1993) and Probabilistic Reversal Learning Task (PRLT; de Ruiter et al., 2009). Decreased response inhibition and increased response perseveration are considered core neurocognitive indicators of elevated compulsivity (Leeman & Potenza, 2012).

## 2.2 Compulsive Traits in Drug Addicts and Genetic Susceptibility

Although research specifically targeting compulsive traits in drug addicts remains limited, early studies focusing on executive or neurocognitive functions have shown that individuals abusing cocaine, cannabis, stimulants, and opioids exhibit widespread deficits in inhibitory control (Bolla et al., 2004; Hester & Garavan, 2004; Rogers & Robbins, 2001). Heroin and cocaine polydrug users demonstrate severe impairments on Stroop cognitive inhibition and card-switching tests (Verdejo-García & Pérez-García, 2007; Fernández-Serrano et al., 2010). Studies have also found that cocaine and methamphetamine users show

marked response perseveration on reversal learning tasks (Ersche et al., 2008; Ersche & Sahakian, 2007; Fillmore & Rush, 2006; Soar et al., 2012), though some studies report inconsistent findings (Goldstein et al., 2004; Madoz-Gúrpide et al., 2011). Meta-analytic evidence indicates that heroin, cocaine, cannabis, and methamphetamine abusers display neurocognitive deficits across multiple domains including inhibitory control, cognitive flexibility, and executive control (Cadet & Bisagno, 2016; Lee et al., 2019; Manning et al., 2017), suggesting that compulsivity-related neurocognitive deficits may represent a common characteristic across different substance use disorders. Comparative studies between substance abusers and gambling addicts reveal similar perseverative tendencies on set-shifting or card-sorting tasks (Leeman & Potenza, 2012). Notably, as a non-substance addictive behavior, gambling disorder shows strong associations with multiple compulsivity-related neurocognitive deficits. Meta-analyses demonstrate that individuals with gambling disorder exhibit significant functional declines on neurocognitive tasks assessing compulsivity, cognitive flexibility, set-shifting, and attentional bias (van Timmeren et al., 2018), indicating that compulsivity may serve as a predisposing factor or potential endophenotypic trait for addictive behaviors (Robbins et al., 2012; van Timmeren et al., 2018). Longitudinal studies show that compulsive traits in childhood and adolescence (e.g., low cognitive flexibility, poor response inhibition) predict substance use disorders in later life, including cannabis, alcohol, and illicit drug dependence (Latvala et al., 2016; Meier et al., 2018; Nigg et al., 2006). These findings underscore the importance of investigating the susceptibility mechanisms of compulsivity in drug addiction, despite its broad cognitive components (Fineberg et al., 2014; Luciano, 2016; Yücel & Fontenelle, 2012).

Regarding genetic susceptibility, family and twin studies reveal that stimulant drug addicts and their drug-naïve siblings show significantly impaired performance on the Stop Signal response inhibition task compared to healthy controls (Ersche et al., 2012a, 2012b), along with structural and functional abnormalities in neural circuits related to motor control and reward anticipation (including medial prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, and dorsal striatum/putamen) (Just et al., 2019), suggesting that response inhibition deficits may represent a potential genetic vulnerability factor or endophenotype for drug addiction. Furthermore, resting-state functional connectivity studies indicate that familial risk for drug addiction is primarily characterized by reduced functional connectivity from orbitofrontal and ventromedial prefrontal cortices to the caudate (a circuit governing goal-directed decision-making), whereas resilience to drug abuse is associated with enhanced connectivity from lateral prefrontal cortex to caudate and supplementary motor area, and from medial prefrontal cortex to putamen (circuits involved in top-down inhibitory control and habit formation) (Ersche et al., 2020). This further demonstrates the critical role of inhibitory control circuits related to compulsivity in addiction development. In situ gene expression and genetic analyses show that reduced dopamine D2 receptor (D2R) gene expression in the dorsal striatum, orbitofrontal cortex, dorsolateral prefrontal cortex, and anterior cingulate may constitute an impor-

tant genetic susceptibility factor for compulsive drug use across substances including alcohol, heroin, cocaine, and methamphetamine (Everitt et al., 2008; Goldman et al., 2005; Volkow et al., 2011). Additionally, reduced expression of the Syn3 gene encoding synapsin III in the dorsal striatum, nucleus accumbens, hippocampus, and prefrontal cortex represents a key genetic mechanism underlying reversal learning impairments and high compulsivity in animal models (Egervari et al., 2018). Epigenetic changes in the catechol-O-methyltransferase (COMT) gene, related to cognitive inhibition and executive function, are also associated with compulsive drug use (Agrawal et al., 2012; Kwako et al., 2018). Research further indicates that epigenetic modifications (e.g., histone modifications, DNA methylation, non-coding RNAs) in multiple brain regions including prefrontal cortex, orbitofrontal cortex, central and basolateral amygdala, dorsal striatum, and nucleus accumbens are closely linked to opioid addiction (Browne et al., 2020). Overall, however, current understanding of the neurocognitive features and genetic susceptibility underlying compulsivity in drug addiction remains limited, necessitating more systematic and in-depth investigation (Lee et al., 2019).

## 2.3 Prefrontal-Anti-reward System Circuits and Compulsivity

From a functional neuroscience perspective, compulsive traits in drug addicts primarily stem from deficits in cognitive top-down control or response inhibition (Dalley et al., 2011), which are associated with dysfunctional projections from the prefrontal cortex to the anti-reward system (Koob & Volkow, 2016). Glutamatergic projections from the prefrontal cortex can directly or indirectly modulate motivation and behavior (Chudasama & Robbins, 2006), while GABAergic dysfunction in the prefrontal cortex may lead to executive dysfunction affecting working memory, self-regulation, and inhibitory control (George et al., 2012; Volkow et al., 2011). Neuroimaging studies show that compulsive features across different drug addictions (e.g., deficient response inhibition, perseverative tendencies, low flexibility) are associated with reduced activation in dorsolateral/ventrolateral prefrontal cortex, dorsal anterior cingulate cortex, and right inferior frontal gyrus, whereas drug-related emotional problems and compulsive actions are linked to medial orbitofrontal cortex and ventral anterior cingulate cortex (Goldstein & Volkow, 2011; Smith & Laiks, 2018). Animal research indicates that the dorsomedial striatum and basolateral amygdala are involved in compulsive drug-seeking behavior (Ostlund & Balleine, 2008), while the prelimbic cortex (homologous to human dorsolateral prefrontal cortex) is implicated in inhibiting drug-seeking behavior (Mihindou et al., 2013). Well-established neural circuits for inhibitory control during tasks like Go/No-Go and Stop Signal include the pre-supplementary motor area in dorsomedial prefrontal cortex, right inferior frontal gyrus in ventrolateral prefrontal cortex, and dorsal striatum (putamen, caudate) (Morein-Zamir & Robbins, 2015). Probabilistic reversal learning involves the circuit from lateral orbitofrontal cortex to ventral striatum, while attentional set-shifting engages the dorsolateral pre-

frontal to ventral striatum circuit (Morris et al., 2016). Additionally, the circuit from lateral orbitofrontal cortex to central amygdala and bed nucleus of the stria terminalis is closely related to unpleasant emotional activation and stress responses, thereby contributing to compulsive drug use (Moorman, 2018; Sinha et al., 2016; Smith & Laiks, 2018). Overall, compulsive mechanisms in drug addiction are inextricably linked to fronto-anti-reward system circuitry, yet systematic investigation of their micro-mechanisms and genetic susceptibility is lacking.

## 2.4 Research Entry Point of This Project

As outlined above, to address the critical scientific question of genetic susceptibility and neurobiological mechanisms in prefrontal-anti-reward system circuits underlying compulsivity in drug addiction, this project will focus on human non-stimulant drug (heroin) addiction. By integrating genetic methods (comparing addicts with their drug-free first-degree relatives such as siblings), neurocognitive and neurophysiological approaches, and neuroimaging techniques, we will explore the role of compulsivity in addiction and its prefrontal-anti-reward system mechanisms: (1) At the neurocognitive level, we will compare compulsivity traits—including compulsive behavioral tendencies, inhibitory control capacity, and cognitive flexibility—among heroin addicts, their healthy drug-free siblings, and normal controls; (2) At the neurophysiological level, we will examine ERP signatures and susceptibility patterns at frontal electrode sites (e.g., N200, P300) during response inhibition and cognitive flexibility tasks across the three groups; (3) Using structural and functional neuroimaging (fMRI), we will analyze structural and functional changes in prefrontal-anti-reward system circuits during inhibitory control tasks, cognitive flexibility tasks, and negative emotion/stress tasks, aiming to explore the genetic susceptibility and neurobiological basis of compulsive mechanisms in drug addiction to support the identification of key biomarkers.

## 3.1 Study 1: Neurocognitive Compulsivity in Heroin Addicts and Genetic Susceptibility Patterns

Previous research suggests that different drug-addicted populations may exhibit abnormal compulsivity profiles (e.g., inhibitory control, cognitive flexibility), yet systematic investigation of their primary manifestations and genetic susceptibility is lacking. This study aims to compare compulsivity features among heroin addicts, their healthy drug-free siblings, and normal controls to reveal hereditary patterns of compulsivity in drug addiction (Ersche et al., 2020). We will recruit 60-80 heroin addicts who have completed physiological detoxification from compulsory isolation rehabilitation centers and community treatment programs in our province. Additionally, we will identify 60-80 drug-free siblings of these addicts through family visits and follow-ups, while recruiting 60-80 matched healthy controls from the community.

**Inclusion criteria:** (1) Heroin addicts: Must meet DSM-5 criteria for opioid use disorder (diagnosed using the Structured Clinical Interview for DSM-5, SCID-5-CV; First et al., 2016) by a clinical psychiatrist and trained clinical psychologist. Participants should be aged 18-50 (Yan et al., 2014), have completed primary school or higher education, possess normal or corrected vision, have no other substance abuse (e.g., cocaine, methamphetamine, MDMA, ketamine), no alcohol abuse/dependence, no history of brain injury or neurological/psychiatric disorders, and have not taken medications affecting neurocognitive function within one week prior to testing; smoking is permitted given common comorbidity. (2) Drug-free siblings of heroin addicts: Must be physically healthy, have never used heroin or other addictive substances, with no alcohol abuse/dependence, brain injury, or neurological/psychiatric history, and no relevant medications within one week; smoking is permitted. Age range 18-50, primary school education or higher, normal vision. (3) Normal controls: Healthy community residents or workers strictly matched demographically to the other groups, aged 18-50, with primary school education or higher, no illegal drug use history, no alcohol abuse/dependence, no brain injury or neurological/psychiatric disorders, no relevant medications within one week, normal vision. All participants will provide informed consent and receive compensation. This study strictly adheres to human subjects research ethics.

We will assess depressive and anxiety symptoms using the Self-Rating Depression Scale (SDS) and Self-Rating Anxiety Scale (SAS) to control for emotional confounds. Compulsivity assessment includes: (1) Inhibitory control tested via Stop-Signal and Stroop color-word conflict tasks; (2) Cognitive flexibility/response perseveration tested via IDED and PRLT tasks. Reduced inhibition and increased perseveration serve as core neurocognitive indicators of high compulsivity. Trait compulsivity will be measured using the PI-WSUR. All cognitive tasks will be computer-administered.

## 3.2 Study 2: Compulsivity in Heroin Addicts and Their Drug-free First-degree Relatives: An ERP Study

To identify neurophysiological biomarkers associated with compulsivity in heroin addiction, this study employs event-related potential (ERP) techniques to examine electrophysiological signatures during response inhibition (Go/No-Go task) and cognitive flexibility (PRLT) tasks in heroin addicts, their drug-free siblings, and normal controls. Following previous research (Campanella et al., 2014; Littel et al., 2012; Luijten et al., 2014), we will record from frontal electrode sites, focusing on N200 and P300 amplitudes and latencies. Each group will comprise 30-40 participants with identical inclusion criteria.

**Procedure:** Participants will be seated in a quiet, electrically shielded laboratory approximately 60 cm from a computer screen. Visual stimuli will be presented randomly with ~300 ms intervals. For example, participants must respond quickly to "circles" (Go trials, ~75%) and withhold responses to "squares" (No-Go trials, ~25%), with practice sessions preceding formal testing.

**Tasks:** (1) Response inhibition (Go/No-Go task): Based on established paradigms (Kim et al., 2017), we will use visual stimuli " " (Go: 450 trials, 75%) and " " (No-Go: 150 trials, 25%) to examine N200 and P300 peak amplitudes and latencies during response inhibition. Regions of interest include frontal sites (F1, Fz, F2) and central sites (C1, Cz, C2) for N200, and parietal (P1, Pz, P2) and central sites for P300. (2) Cognitive flexibility (PRLT): Using the classic paradigm (de Ruiter et al., 2009), participants will choose between paired object images (e.g., car vs. tie). After establishing a stimulus-outcome association (>90% accuracy), the contingency reverses (e.g., choosing the car now results in loss), measuring how many errors occur before learning the new rule. The feedback-related negativity (FRN, ~250-300 ms post-stimulus) originating from the anterior cingulate cortex (ACC) is thought to correlate with successful reversal learning (Chase et al., 2011; Luijten et al., 2014).

### 3.3 Study 3: Compulsivity in Heroin Addicts and Prefrontal-Anti-reward System Mechanisms: An fMRI Study

To further explore the neurobiological basis of compulsivity in drug addiction, this study uses structural and functional neuroimaging (MRI & fMRI) to compare brain changes in prefrontal-anti-reward circuits during inhibitory control and negative emotion activation tasks among heroin addicts, their drug-free siblings, and normal controls. Each group will include 30-40 participants with identical inclusion criteria. Tasks include our established Go/No-Go task and the Analogic Social Exclusion Task (ASET) fMRI paradigm.

**Task procedures:** (1) Go/No-Go task: Participants respond to two colored rectangles (blue, green) in horizontal or vertical orientation. Blue rectangles (75%, 300 trials) are Go trials; green rectangles (25%, 100 trials) are No-Go trials. Stimuli appear for 1200 ms, preceded by a fixation cross (1000-1800 ms) and followed by a blank screen (1000-1800 ms). Trials are pseudorandomly presented with practice sessions. (2) ASET: Adapted from classic social exclusion paradigms (Eisenberger et al., 2003), this task induces social affective distress or social stress to activate right ventral prefrontal cortex (vPFC), orbitofrontal cortex (OFC), dorsal anterior cingulate cortex (dACC), and central amygdala (CeA). In a paired-character game, participants make choices during two phases: social inclusion (all choices receive positive feedback: virtual monetary rewards or encouraging responses) and social exclusion (75% probability of negative feedback: monetary loss, disdainful expressions, boos, rejection gestures). After scanning, participants complete a social affective distress self-rating scale (7-point Likert) assessing feelings of rejection and invisibility (Eisenberger et al., 2003).

We will use Tract-Based Spatial Statistics (TBSS) to compare white matter fiber density (fractional anisotropy, FA) and Voxel-Based Morphometry (VBM) to compare gray matter density in regions of interest (ROIs) across groups. ROIs

are selected based on the prefrontal-anti-reward circuit: dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), inferior frontal gyrus (IFG), ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), ventral striatum (nucleus accumbens), dorsal striatum (caudate, putamen), central amygdala (CeA), and bed nucleus of the stria terminalis (BNST). Event-related fMRI will analyze activation differences in these ROIs during task performance. We will also correlate ROI activation with PI-WSUR scores to explore genetic biomarkers of compulsivity.

## 4. Expected Results and Theoretical Framework

Focusing on the core question of genetic susceptibility and prefrontal-anti-reward circuit neurobiology underlying compulsivity in drug addiction, this project examines heroin addiction from a family-risk perspective, integrating neurocognitive, neurophysiological, and neuroimaging methods to identify neurobiological markers and potential intervention targets (Severino & Evans, 2019).

We expect that at the neurocognitive level (Study 1), heroin addicts will show inhibitory control deficits on tasks like Stop-Signal (Su et al., 2020), similar to other drug-addicted populations (Liu et al., 2019), and increased response perseveration on reversal learning tasks (Yang et al., 2018). While no evidence yet indicates deficits in healthy siblings of heroin addicts, robust findings from stimulant addiction research (Ersche et al., 2012a, 2020) lead us to predict that siblings may also show some degree of inhibitory control impairment or perseverative tendency, suggesting a potential hereditary risk for compulsivity in drug addiction (Lee et al., 2019). At the neurophysiological level (Study 2), we anticipate abnormal N200 and P300 latencies and amplitudes during response inhibition in heroin addicts (Su et al., 2017; Zheng et al., 2020), and abnormal FRN during reversal learning (Riesel et al., 2019). These ERP components, as potential neurophysiological markers of addiction (Habelt et al., 2020), may also show abnormalities in siblings. At the neuroimaging level (Study 3), we expect heroin addicts to show inhibitory control circuit abnormalities during Go/No-Go tasks, including reduced activation in dlPFC, dACC, and right IFG alongside hyperactivity in dorsal striatum (Zilverstand et al., 2018). During negative emotion activation (ASET), we anticipate reduced activation in medial PFC and OFC and increased activation in ventral striatum/nucleus accumbens and CeA. These functional changes should correspond to structural abnormalities in these ROIs (e.g., altered white matter integrity and gray matter density). By comparing addicts, siblings, and controls, we expect to identify familially susceptible neuroimaging markers associated with compulsivity (Ersche et al., 2020).

Based on these anticipated findings, we propose a preliminary theoretical model of compulsivity and prefrontal-anti-reward circuit dysfunction in heroin addiction: (1) Neurocognitive deficits related to compulsivity (e.g., inhibitory control, set-shifting, reversal learning) may serve as potential markers for heroin

addiction, representing familial vulnerability factors present in both addicted individuals and their healthy siblings (Ersche et al., 2020; Lee et al., 2019; van Timmeren et al., 2018). (2) At the neural level, abnormalities in key ERP components (N200, P300, FRN) (Habelt et al., 2020) and structural-functional alterations in prefrontal-anti-reward circuits (e.g., cognitive control circuits: dlPFC/dACC/rIFG to dorsal striatum; emotional regulation circuits: mPFC/OFC to CeA) may constitute the neurobiological basis of compulsivity and its genetic susceptibility in drug addiction (Lüscher et al., 2020).

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