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IMPULSIVUTY AND NEGATIVE AFFECTIVITY IN OPIATE DEPENDENT INDIVIDUALS IN DIFFERENT STAGES OF PROTRACTED ABSTINENCE

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INTRODUCTION

Opiate dependence and related severe impairments in neurocognitive and emotional functioning have generated increased scientific interest in recent decades, particularly in the context of the challenges associated with the ongoing opiate crisis in the United States. One of the most understudied topics in the literature is specifically related to the assessment of the relative stability or reversibility of impairments in the cognitive and affective domains. The question of whether cognitive and affective deficits persist even in the stages of protracted abstinence following chronic opiate use remained unanswered. Research focusing on the role of certain dimensions of neurocognitive and affective functioning in the understudied stage of long-term abstinence hold the potential for uncovering clinically relevant patterns that may have real-world practical implications in addiction treatment and rehabilitation, as well as in the development of novel, personalized interventions targeting people who suffer from substance use disorders.

Impulsivity and impairments in inhibitory control are widely studied in addiction literature, as they are strongly affected by the use of different classes of psychoactive drugs (Kwako et al., 2016). *Impulsivity* has both personality and neurocognitive dimensions that are differentially involved in the processes of initiation of substance use and maintenance of substance dependence, but these impulsivity dimensions may also exert additional effects in the stages of early and protracted abstinence. A number of studies in the field have suggested that increased levels of both personality and neurocognitive impulsivity may have additional negative effects on addictions treatment (Passetti et al., 2008; 2011; Paulus et al., 2005; Poling et al., 2007), placing them at the core of potential targets for future highly personalized interventions for working with people suffering from addictions.

Negative affectivity is another key neurofunctional domain that plays a fundamental role in both the onset and progression of addictions and in the mechanisms associated with recovery and maintenance of protracted abstinence (Heilig & Koob, 2007; Koob, 2020; Kwako et al., 2016). Studies in the field have reported that increased *negative affectivity* is consistently associated with serious challenges to both treatment effectiveness and the individual ability to sustain long-term remission (Erfan et al., 2010; Lejuez et al., 2008; Palma-Álvarez et al., 2021a; Wolitzky-Taylor et al., 2011).

Despite the rich body of research illustrating the importance of distinct dimensions of *impulsivity* and *negative affectivity* in the mechanisms of addictions, our knowledge of the specific role of these two neurofunctional domains in the protracted abstinence stage of the addiction cycle is still limited. The majority of previous studies in the field were based on samples of active users or individuals within one

year of abstinence, which hinders the identification of potential impairments or resources in *impulsivity* and *negative affectivity* in the stages of longer-term protracted abstinence. In addition, the vast majority of studies used samples consisting of individuals who met criteria for more than one substance use disorder (i.e., polydependence) or were enrolled in pharmacologically mediated treatments. These limitations prevent us from drawing stable conclusions associated with the specific effects of different classes of psychoactive substances on the dimensions of *impulsivity* and *negative affectivity*. In addition, opiate dependence is significantly less researched compared to stimulant or alcohol dependence (Verdejo-García et al., 2008; Zeng et al., 2013), which further hinders the development of more effective interventions targeting opiate dependent individuals.

In light of the identified limitations of prior research, the current study was focused on examining various components of *impulsivity* (trait impulsivity, impulsive choice, impulsive action) and *negative affectivity* (depression, anxiety, anxiety sensitivity, and alexithymia) among opiate dependent individuals who successfully maintained different periods of abstinence – short-term abstinence [< 12 months] and long-term abstinence [> 12 months]. Identifying specific impairments in neurocognitive and affective functioning among individuals who successfully maintain protracted abstinence may be key to the development of individualized rehabilitation programs targeted at strengthening cognitive function and improving emotion regulation.

CHAPTER ONE. SUBSTANCE USE DISORDERS

The most commonly accepted definition in the literature conceptualized addictions as chronic and relapsing brain disorders that are characterized by: (1) compulsion to seek and administer the psychoactive drug, (2) loss of control in limiting intake of the psychoactive drug, and (3) the emergence of acute negative emotional states when there is no access to the drug (Koob, 2006; Koob & Le Moal, 1997). Addiction has been increasingly defined in a progressive framework, with a number of researchers emphasizing that the development of substance use disorder is the final stage in the transition from impulsive to compulsive patterns of chronic substance use (Heilig & Koob, 2007). This transition is marked by specific changes in brain function and consequent alterations in motivation to use substances.

Addiction evolves through three main spiraling stages - *binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/ anticipation* - associated with dysregulation and neuroadaptations in specific neural circuits reflecting impairments in three key neurofunctional domains - *incentive salience*, *negative affect*, and *executive functions* (Koob, 2020; Kwako et al., 2016). Neuroadaptations in the *binge/intoxication*

stage are associated with specific impairments in *incentive salience*, reflecting dopaminergic activations in the basal ganglia. The *withdrawal/negative affect* stage is marked by a significant exacerbation of negative affectivity associated with increased activation of the brain stress systems such as the extended amygdala, and the *preoccupation/anticipation* stage is primarily associated with impairments in a range of executive functions arising from reduced functionality of prefrontal brain regions (Kwako et al., 2016; 2017).

Current research in the field has been increasingly focused on systematic assessment of impairments in *incentive salience*, *negative affectivity*, and *executive functions*, as these neurofunctional domains are severely affected by the use of different classes of psychoactive substances and are simultaneously conceptualized as key explanatory factors of the relapsing nature of addictions (Kwako et al., 2016).

Among the most significant gaps in the literature on addictions is the limited understanding of the mechanisms involved in the protracted abstinence stage of the addiction cycle and the underestimation of the need to conduct research examining the neurobiological, neuropsychological, and behavioral correlates of addiction in different periods of the protracted abstinence stage. Much of the research in the field is focused on the acute withdrawal stage or examined changes occurring up to several weeks after the reduction of the physical discomfort accompanying the withdrawal syndrome, with an extremely small number of studies examining the specifics of the three neurofunctional domains in the protracted abstinence stage.

The findings of the small number of previous studies are highly conflicting, with some studies reported relative recovery across the three neurofunctional domains (Bensmann et al., 2019; Farhadian et al., 2017; Kim et al., 2006; Salo et al., 2009; Stock et al, 2019), while others have found that impairments in *incentive salience*, *executive functions*, and *negative affectivity* are long-term and persistent and are not significantly affected by the length of abstinence (Fitzpatrick et al., 2021; Lee & Pau, 2002; Volkow et al., 2001b).

CHAPTER TWO. VARIETIES OF IMPULSIVITY IN SUBSTANCE USE DISORDERS

Impulsivity is among the core dimensions of the broader category of *executive functions* identified as one of the key neurofunctional domains severely affected by substance use (Kwako et al., 2016). Impulsive and compulsive behaviors are seen as core aspects of substance use disorders that are not only involved in individual vulnerability to addictions, but contribute significantly to the individual difficulties in maintaining long-term abstinence (Lee et al., 2019).

Impulsivity has been increasingly conceptualized as a multifactorial construct that involves several dimensions related to different forms of impulsive behavior which are mediated by distinct neural pathways (Evenden, 1999). Current models of *impulsivity* distinguish three main latent dimensions in its structure: (1) *impulsivity* as a stable personality trait; (2) *impulsivity* as a neurocognitive dimension; and (3) *impulsivity* as a feature of a broad range of psychiatric disorders associated with the so-called externalizing spectrum (Evenden, 1999; MacKillop et al., 2016; Vassileva & Conrod, 2019). Neurocognitive *impulsivity* is additionally subdivided into two broad domains: (1) *impulsive action* (Hamilton et al., 2015a), involving deficits in rapid response inhibition, and (2) *impulsive choice* (Hamilton et al., 2015b), indicating deficits in reward-based decision-making.

Recent studies on *impulsivity* and substance use disorders have emphasized the need to address the multidimensional nature of both *impulsivity* and drug addictions, as this could lead to the discovery of specific dimensions of impulsive behavior that are involved in the development and maintenance of addictions to different classes of psychoactive substances (Vassileva & Conrod, 2019), as well as to clarifying the role of *impulsivity* in the significantly understudied stage of protracted abstinence.

Although there has been a notable interest in the specific effects of different classes of psychoactive substances on neurocognitive function, the role of *impulsivity* has been thoroughly investigated primarily within the framework of stimulant dependence (Verdejo-García et al., 2008), whereas studies on *impulsivity* and opiate addiction have been limited and produced inconsistent and inconclusive findings (Zeng et al., 2013). The predictive validity of distinct *impulsivity* dimensions with respect to a number of clinically relevant characteristics of addictive behavior (e.g., relapse, adherence to treatment plan, treatment outcome) required their further investigation within the framework of opiate addiction. In addition, only a small number of studies were focused on the specifics of neurocognitive functioning in opiate dependent individuals who maintain successful and long-term abstinence, despite their potential to inform the development of novel, highly effective therapeutic interventions that can be translated into the treatment of opiate dependence. The majority of previous studies in the field, investigating distinct dimensions of *impulsivity* in the early abstinence stage of opiate addiction, uncovered persistent impairments in inhibitory control and decision-making (Ahn et al., 2014; Fishbein et al., 2007; Fu et al., 2008; Kriegler et al., 2019; Lee & Pau, 2002; Liao et al., 2014; Sun et al., 2015). However, the focus on relatively short periods of abstinence (i.e., up to 12 months) hinders the dissociation of the acute effects of intoxication or the direct pharmacological effects of opiates on the potential deficits in *impulsivity* that may characterize the stages of protracted abstinence and thus represent a potential risk for relapse even

after long-term recovery. In order to address these significant gaps in the literature, one of the aims of the present study was specifically related to the assessment of a wide range of *impulsivity* dimensions (i.e., personality, psychiatric, neurocognitive) among opiate users in different stages of protracted abstinence, ranging from 30 days to 9 years. This would provide a more comprehensive understanding of the specific impairments and potential resources in executive functioning among individuals who maintain successful abstinence following chronic opiate addiction.

CHAPTER THREE. NEGATIVE AFFECTIVITY IN SUBSTANCE USE DISORDERS

Although a massive body of addiction research was focused on elucidating the specific role of *impulsivity* and reward-mediating brain circuits in substance use disorders, impairments in the affective domain are crucial building blocks in the development of a deeper understanding of the pathology of addictions (Koob et al., 2014). *Negative affectivity* is one of the fundamental aspects of drug addictions, which is conceptualized as a core mechanism in both the onset and maintenance of substance use disorders and the vulnerability to relapse following periods of prolonged abstinence (Kassel et al., 2007; Koob & Le Moal, 2008; Koob & Volkow, 2016). *Negative affectivity* has been defined as a global affective dimension associated with the experience of subjective distress and the emergence of various emotional states that are unpleasant and have a negative valence (e.g., fear, anxiety, depression, irritability) (Watson et al., 1988). *Negative affectivity* is often viewed as a more general term that encompasses various distinct but interrelated categories of negative emotional states. The focus of the current study was placed on four major *negative affectivity* dimensions - *depression*, *anxiety*, *anxiety sensitivity*, and *alexithymia* - that may significantly improve our understanding of the specifics of emotional functioning in addictions as well as in different stages of protracted abstinence.

Current neurobiological models of substance use disorders have emphasized that *negative affectivity* has a key role particularly in opiate addiction (Emery & Akil, 2020; Koob, 2020; Shurman et al., 2010; Welsch et al., 2020). The majority of researchers in the field have recognized *negative affectivity*, similar to *impulsivity*, as both a cause and a consequence of chronic substance use. In addition to its role as a risk factor predisposing to various substance use disorders, *negative affectivity* is strongly implicated in the *withdrawal/negative affect* stage of the addiction cycle, reflecting neuroadaptations in the reward system and the brain stress systems that occur following chronic substance use (Koob, 2009; Koob & Le Moal, 2001). *Negative affectivity*, associated with excessive *anxiety*, *depression*, emotional pain, and *alexithymia*, characterizes the acute withdrawal state and appears to persist even in the protracted

abstinence stage of the addiction cycle, increasing the individual vulnerability to relapse even after long-term sustained remission (Heilig & Koob, 2007; Koob, 2020).

Previous studies examining different dimensions of *negative affectivity* reported an overall decline in *depression* in both short-term (Krupitsky et al., 2016; Momeni et al., 2010; Shi et al., 2009) and long-term abstinence (Stapleton, & Comiskey, 2011; Havard et al., 2006; Darke et al., 2009). On the other hand, *anxiety*, *anxiety sensitivity*, and *alexithymia* appear to be consistently elevated in both early (Ayhan et al., 2020; Craparo et al., 2016; Gerra et al., 2014; Lejuez et al., 2006) and protracted abstinence (Psederska et al., 2019; Stapleton & Comiskey, 2011; Torrado et al., 2013). These findings suggest that *negative affectivity* is among the core characteristics of opiate addiction closely related to the withdrawal stage of the addiction cycle and the processes of recovery and sustained remission. Negative emotional states are attracting increasing attention in current research and were acknowledged as potential targets of various prevention programs and treatment interventions, but are rarely addressed in traditional opiate dependence treatments. The development of individualized interventions aimed at addressing the most pronounced domains of *negative affectivity* could be of particular relevance in the context of the widespread opioid crisis and the critical need to create more effective therapeutic alternatives for treating opiate dependence. For this reason, in addition to assessing distinct *impulsivity* dimensions, the current study also aimed to examine a wide range of negative affective states (*depression*, *anxiety*, *anxiety sensitivity*, and *alexithymia*) among individuals in different stages of protracted abstinence. Such studies, albeit cross-sectional, could provide valuable information about the possible effects of length of abstinence on clinically relevant characteristics of addictions such as *impulsivity* and *negative affectivity*, which are consistently associated with increased risk of relapse and return to chronic opiate use even after long-term abstinence.

CHAPTER FOUR. METHODOLOGICAL LIMITATIONS OF PRIOR RESEARCH ON IMPULSIVITY AND NEGATIVE AFFECTIVITY IN OPIATE DEPENDENT INDIVIDUALS.

Despite undeniable advances in current empirical approaches to addiction, several major methodological problems can be identified that limit the conclusions of previous studies in the field.

Effects of different classes of psychoactive drugs and the high prevalence of polysubstance dependence

One of the main sources of individual differences in neurocognitive and emotional functioning among substance dependent individuals may be related to the long-term pharmacological and toxicological effects of different classes of psychoactive substances. Early research in the field of addiction was based

on extremely heterogeneous samples consisting of individuals dependent on various classes of psychoactive drugs who actually had very little in common. One possible explanation for the major inconsistencies across findings produced by these early studies is their inability to form more homogeneous and coherent samples. Although many researchers acknowledged that addiction research should be focused on more homogeneous research samples, studies often fail to account for the effects of distinct classes of psychoactive substances on *impulsivity* and *negative affectivity*. With few exceptions, the vast majority of studies examining the main dimensions of *impulsivity* and *negative affectivity* among substance users were based on samples consisting of polysubstance dependent individuals who reported a marked preference for a particular class of psychoactive substances (e.g., opiates or stimulants) but have comorbid substance use disorders. Thus, one of the major goals of future studies on addictions should be the recruitment of highly homogeneous samples including "pure" groups of individuals who are dependent on only one specific class of psychoactive substances (i.e., mono-dependent individuals). Such research may provide a deeper understanding of the specifics of *impulsivity* and *negative affectivity* in the narrower context of a particular type of addiction.

Effects of heterogeneity related to different stages of addiction and length of abstinence

Another common methodological problem in empirical approaches to addiction is associated with the high heterogeneity of research samples used in the majority of studies on *impulsivity* and *negative affectivity* among opiate dependent individuals. There is a wide variation in sample selection, ranging from studies based on active users, individuals enrolled in pharmacologically maintained treatment or individuals in short-term non-pharmacologically mediated abstinence [up to 12 months], to the limited number of studies based on samples composed of opiate users who maintain successful long-term abstinence [for more than 12 months]. Not surprisingly, findings in the field of opiate addiction are extremely conflicting.

Contemporary approaches in addiction research emphasized the growing need for a deeper understanding of the underlying mechanisms and processes involved in protracted abstinence [i.e., more than 12 months], one of the least well-understood stages of the addiction cycle. Such research may provide pivotal information related to the potential recovery of certain functions associated with *impulsivity* and *negative affectivity* with abstinence from opiate use, as well as to elucidate the chronic and persistent impairments that do not seem to be affected by length of abstinence.

CHAPTER FIVE. EMPIRICAL STUDY

OBJECTIVES AND HYPOTHESES

Objectives

The main aim of the present study was to examine the profiles of impairments and resources in two of the three basic neurofunctional domains that could expand our knowledge about recovery from chronic opiate addiction. The main neurofunctional domains of interest for the current study are *executive functioning*, specifically *impulsivity* (with its personality, psychiatric, and neurocognitive dimensions), and *negative affectivity*, and its underlying dimensions (*depression*, *anxiety*, *anxiety sensitivity*, and *alexithymia*). The goals of the current study can be divided into two main categories: **Objective 1** was focused on examining the long-term (residual) effects of opiate dependence on distinct dimensions of *impulsivity* and *negative affectivity* among opiate users in different stages of protracted abstinence (i.e., short-term [<12 months] and long-term [>12 months]), whereas **Objective 2** was specifically focused on assessing the effects of length of abstinence on the main dimensions of *impulsivity* and *negative affectivity*. To address the main methodological limitations of previous studies on addiction, we recruited a sample of opiate mono-dependent individuals who had no history of co-occurrent substance use disorders, and were not enrolled in pharmacologically mediated treatment at the time of testing. In addition, the study implemented a rich research battery that aims to capture a wide range of *impulsivity* and *negative affectivity* dimensions.

Hypotheses

Based on the reviewed findings produced by prior research, we propose the following main hypotheses:

Objective 1. To examine the long-term (residual) effects of opiate dependence on distinct dimensions of *impulsivity* and *negative affectivity* among opiate users in different stages of protracted abstinence (short-term [<12 months] or long-term [>12 months].

Hypothesis 1. There will be specific group differences in *impulsive choice*, *trait impulsivity* and *psychopathy*.

Hypothesis 1A. Regardless of length of abstinence, opiate users will be characterized by poorer performance on *impulsive choice* tasks and elevated *trait impulsivity* and *psychopathy* compared to control participants.

Hypothesis 1B. The group of opiate dependent individuals in short-term abstinence will show poorer performance on *impulsive choice* tasks compared to the group of opiate dependent individuals in long-term abstinence.

Hypothesis 1C. We expect no group differences in levels of *psychopathy* and *trait impulsivity* between opiate dependent individuals in short-term and long-term abstinence.

Hypothesis 2. To test for group differences in performance on *impulsive action* tasks.

Hypothesis 2A. To examine whether opiate dependent individuals in short-term and long-term abstinence will be characterized by poorer performance on *impulsive action* tasks compared to the control group.

Hypothesis 2B. To examine whether differences in performance on *impulsive action* tasks will be observed between groups of opiate dependent individuals in short-term and long-term abstinence.

Hypothesis 3. There will be specific group differences in distinct *negative affectivity* dimensions.

Hypothesis 3A. Regardless of length of abstinence, opiate dependent individuals will be characterized by increased *negative affectivity* (i.e., *depression*, *anxiety*, *anxiety sensitivity*, and *alexithymia*) compared to the control group.

Hypothesis 3B. Opiate dependent individuals in long-term abstinence will be characterized by lower levels of *depression* relative to opiate dependent individuals in short-term abstinence; *anxiety*, *anxiety sensitivity*, and *alexithymia* will be common in both stages of protracted abstinence.

Objective 2. To examine the effects of length of abstinence on distinct indices of *impulsivity* and *negative affectivity*.

Hypothesis 1. Length of abstinence will be associated with better performance on *impulsive choice* tasks.

Hypothesis 2. Length of abstinence will have no specific effects on performance on *impulsive action* tasks.

Hypothesis 3. Length of abstinence will have no specific effects on *trait impulsivity* and *psychopathy*.

Hypothesis 4. Length of abstinence will be associated with reduced *depression*, but will have no specific effects on other dimensions of *negative affectivity* (i.e., *anxiety*, *anxiety sensitivity*, and *alexithymia*).

METHOD

Design

The study employed a quasi-experimental, cross-sectional between-group design.

The main independent variables (IVs) were grouped into the following categories:

(1) Demographic variables: 1) Research group (three levels: control group, opiate dependent individuals in short-term abstinence, opiate dependent individuals in long-term abstinence); 2) Gender (two levels: male gender and female gender); 3) Age (measured in years)

(2) Fluid intelligence (Estimated IQ score on Raven's Standard Progressive Matrices)

(3) Variables associated with opiate use: 1) Length of abstinence (measured in days); 2) Severity of opiate dependence (number of DSM-IV opiate dependence symptoms); 3) Duration of opiate dependence (measured in days)

Dependent variables (DVs) were grouped into the following main categories:

(1) Personality and psychiatric indices of impulsivity: 1) Trait impulsivity (measured by *UPPS Total score*); 2) Psychopathy (measured by *PCL:SV Factor 1*, *PCL:SV Factor 2*, and *PCL:SV Total score*)

(2) Impulsive choice domain: 1) Decision-making under ambiguity (as measured by the *IGT Net score*); 2) Decision-making under risk (as measured by the *CGT Quality of decision-making* index); 3) Temporal reward discounting (as measured by the *MCQ Overall k* index)

(3) Impulsive action domain: 1) Action restraint (measured by the *GNG False alarms* index); 2) Action cancellation (measured by the *SST 150 ms Inhibition* index); 3) Reaction time (RT) in response inhibition tasks (measured by the *SST 150 ms Reaction Time* index)

(4) Negative affectivity domain: 1) Depression (measured by BDI-II Total score); 2) Anxiety (measured by STAI-Y Total state and trait anxiety scores); 3) Anxiety sensitivity (measured by ASI Total score); 4) Alexithymia (measured by TAS-20 Total score)

Participants and Procedures

Data was collected as part of a larger international ongoing study investigating different types of *impulsivity* in opiate and stimulant users. The study was supported by grant R01 DA021421 from the National Institute on Drug Abuse (NIDA) and the Fogarty International Center (FIC), with principal investigator Assoc. Prof. Jasmin Vassileva, PhD. Measures of *impulsivity* and *negative affectivity* were part

of a larger research battery including a combination of clinical interviews, self-report questionnaires, and neurocognitive tests. The study was organized into three main steps: 1) a telephone screening interview with potential research participants; 2) a first study session (approximately 3.5 hours); and 3) a second study session (approximately 3.5 hours); study sessions were conducted on two separate days.

The current sample consisted of 181 participants between the ages of 21 and 48 years. 113 participants met DSM-IV criteria for lifetime mono-dependence on heroin, of whom 45 (39.8%) were in short-term abstinence [<12 months] and 68 (60.2%) were in long-term abstinence [>12 months]. The control group included 17 (25%) females and 51 (75%) males who had no history of substance abuse or dependence. The group of participants in short-term abstinence included 9 (20%) females and 36 (80%) males who maintained abstinence for a mean of 6.56 (SD = ±3.76) months (range 30 days to 365 days). The group of participants in long-term abstinence included 13 (19.1%) females and 55 (80.9%) males who maintained abstinence for a mean of 4.40 (SD = ± 2.52) years (395 days to 3285 days (9 years).

Instruments

Substance dependence. Substance dependence was assessed using the *Structured Clinical Interview for DSM-IV-Substance Abuse Module* (SCID-SAM; First et al., 1996), designed to determine whether an individual meets criteria for any substance use disorder according to the DSM-IV. The interview was primarily used to assign participants to the different study groups. In addition, we used several key indices of opiate use for the specific aims of the current study: 1) severity of opiate dependence (i.e., number of opiate dependence symptoms met); 2) duration of opiate dependence (in days); and 3) length of abstinence (in days).

Psychopathy. The *Psychopathy Checklist: Screening Version* (PCL:SV; Hart et al., 1995) is a semi-structured interview which involves the assessment of 12 features of *psychopathy* divided into two main factors: 1) interpersonal and affective characteristics of *psychopathy* (e.g., grandiosity, manipulativeness) and 2) impulsive and antisocial domain of *psychopathy* (e.g., impulsivity, irresponsibility). Items are scored on a three-point scale (0 = absent, 1 = somewhat present, 2 = definitely present) and summed to form a total score ranging from 0 to 24 points.

Fluid intelligence. *Raven's Standard Progressive Matrices* (Raven et al., 2000) were used to measure *fluid intelligence*. The instrument consists of 60 multiple-choice visual items, divided into five sets of 12 items each. The test items within each set are listed in order of increasing difficulty. All of the items presented a pattern of shapes with a missing piece. The participant is asked to identify the missing element, which

completes the pattern of shapes by choosing one out of six or eight options for each item. Estimated IQ score ranges from 55 to 132 points.

Trait Impulsivity. The *UPPS Impulsive Behavior Scale* (UPPS; Whiteside & Lynam, 2001) is a self-report questionnaire measuring four distinct dimensions of *trait impulsivity*. The UPPS consists of 45 items rated on a 4-point Likert scale. The four UPPS subscales reflect different dimensions of impulsive behavior: *urgency*, (lack of) *perseverance*, (lack of) *premeditation*, and *sensation seeking*. The UPPS total score ranges from 45 to 180 points.

Impulsive choice domain. To investigate the *impulsive choice* domain, we employed three separate neurocognitive tasks that capture its distinct components: (1) decision-making under ambiguity; (2) decision-making under risk; and (3) temporal reward discounting.

- *The Iowa Gambling Task* (IGT; Bechara et al., 1994; 2000) is a computerized neurocognitive task that measures decision-making under uncertainty and requires learning by trial-and-error. Examinees are presented with four decks of cards and instructed to select cards to maximize earnings. Decks A and B are associated with higher rewards but also higher occasional penalties. Selecting from Decks C and D yields lower rewards and lower occasional penalties and thus reflecting more advantageous long-term strategy. The IGT consists of five blocks of 20 choices each. The performance indices used in the current study were: 1) *IGT Net score*, reflecting the total number of advantageous choices minus the total number of disadvantageous choices (values range from -40 to 60 points); 2) the net scores of the five separate blocks of the task (*IGT Block 1*; *IGT Block 2*; *IGT Block 3*; *IGT Block 4*; *IGT Block 5*).
- *The Cambridge Gambling Task* (CGT; Rogers et al., 1999) is a computerized neurocognitive task that assesses risky decision-making, which does not involve learning. Examinees are presented with 10 boxes colored red or blue and are asked to guess whether a yellow token is hidden under a red or a blue box. The ratios of red:blue boxes vary from 1:9 to 9:1 in pseudorandom order. Participants earn points based on correct performance. The second phase of the task asks participants to gamble points based on the confidence of their decisions, by selecting from an array of bets ranging from 5 to 95% of their earned points, presented in ascending and descending order. For the purposes of the current study, we used the *CGT Quality of decision-making* index, which reflects betting on the more likely outcome of the two possible alternatives (i.e., red or blue boxes), as assessed by the percentage of instances in which the participant bet on the color that has the higher box ratio.

- *The Monetary Choice Questionnaire* (MCQ; Kirby et al., 1999) was used to measure delay discounting. The MCQ is a self-report questionnaire that consists of 27 choices between smaller rewards available on the day of testing and larger rewards available from 1 week to 6 months in the future, thereby capturing the tendency to discount rewards that are delayed in time. The 27 questions were grouped in one of three categories based on the approximate magnitudes of the delayed rewards: small ($25–35), medium ($50–60) and large ($75–85). The *MCQ Overall k* index was used to reflect the delay discounting rate (values range from 0.0003 to 0.2500 points).

Impulsive action domain. To assess the *impulsive action* domain, we administered two separate neurocognitive tasks that capture different components of response inhibition: (1) action restraint (i.e., automatic inhibition) and (2) action cancellation (i.e., controlled inhibition).

- *The Go/No-Go Task* (GNG; Lane et al., 2007) is a computerized measure of response inhibition in conditions of varying difficulty (i.e., *automatic inhibition*). A series of two-element visual stimuli arrays are presented on a screen for 500ms and examinees are instructed to respond when the two elements are identical ("Go") and to inhibit responding when the stimuli are discrepant ("No-Go"). Errors of commission errors (*GNG False alarms*), measuring incorrect responding to a non-target stimulus were used as an index of response disinhibition.
- *The Stop Signal Task* (SST; Dougherty et al., 2003; 2005) is a stop-signal paradigm examining *controlled inhibition*, which presents examinees with a series of five-digit numbers displayed for 500ms each. Examinees are instructed to respond when a stimulus is identical to the previous display ("Go") and to withhold responding when the stimulus matches, but then changes color from black to red ("Stop"). Stop signals occurred at 50, 150, 250, and 350ms intervals after the appearance of the target "go" stimulus. The performance measures used in the analyses were: 1) *SST 150ms Inhibition* ratio, calculated by dividing the failures to inhibit a response on "Stop trials" by correct detections on "Go trials" at the 150ms stop-signal delay; 2) *SST 150ms Reaction Time* (ms) which estimates the mean reaction time in the "Go trials" in which the subject responded correctly to a target stimulus.

Depression. The *Beck Depression Inventory-II* (BDI-II; Beck et al., 1996) is a 21-item scale that measures severity of *depression* symptoms during the last 2 weeks and asks participants to rate the extent to which they endorse each symptom on a four-point Likert Scale. Total scale scores ranged from 0 to 63.

Anxiety. The Spielberger *State-Trait Anxiety Inventory* (STAI; Spielberger et al., 1983) is a self-report instrument with two sections, each comprised of 20 items. The first section measures situational "state" anxiety, whereas the second one measures anxiety as a relatively stable personality trait. Answers are scored on a four-point Likert scale, with values on each of the two subscales ranging from 20 to 80 points.

Anxiety sensitivity. The *Anxiety Sensitivity Index* (ASI; Reiss et al., 1986) is a self-report questionnaire that includes 16 items rated on a five-point Likert scale. Higher scores reflect stronger negative emotions associated with the experience of *anxiety*. The ASI total score ranges from 0 to 64 points.

Alexithymia. The *Toronto Alexithymia Scale-20* (TAS-20; Bagby et al., 1994a, b) is a self-report measure of *alexithymia* that consists of 20 items rated on a five-point Likert scale. The *TAS-20 Total score* ranges from 20 to 100 points.

RESULTS

Objective 1.

To examine the long-term effects of opiate dependence on different dimensions of *impulsivity* and *negative affectivity* (**Objective 1**), we conducted multiple analyses to test for group differences between the two groups of abstinent opiate users and the control group.

Impulsivity

<u>Impulsive choice</u>

Data analyses revealed that the three study groups differed significantly on all *impulsive choice* dimensions: 1) decision-making under risk (*CGT Quality of decision making* [$H_{(2)}$ = 10. 45, p = .005, ε^2 = .059]), 2) temporal reward discounting (*MCQ Overall k* [$H_{(2)}$ = 14.30, p = .001, ε^2 = .079]), and 3) decision-making under ambiguity (*IGT Net score* [$F_{(2,172)}$ = 4.43, p = .013, η_p^2 = .049]). Additional post hoc analyses for pairwise comparisons showed that the control group was characterized by better decision-making in both risky (CGT) and ambiguous (IGT) context compared to opiate users in short-term abstinence ($p < .01$). On the other hand, both groups of opiate dependent participants were characterized by increased delay discounting (MCQ) relative to the control group ($p < .05$), while differences on temporal reward discounting between the two opiate groups were non-significant ($p > .05$).

Table 1 provides descriptive statistics and group differences in indices of *impulsive choice*.

Table 1. Group differences in indices of impulsive choice.

	Controls (1)	Short-term abstinence (2)	Long-term abstinence (3)	*p*	Contrast
N	66	44	66	-	
CGT Quality of decision-making	0.91 (0.10)	0.83 (0.16)	0.87 (0.14)	**.005**	1 > 2
N	63	39	64		
MCQ Overall k	0.048 (0.073)	0.086 (0.081)	0.075 (0.087)	**.001**	1 < 2, 3
N	67	43	65		
IGT Net score	10.04 (26.97)	-4.74 (19.65)	1.37 (28.95)	**.013**	1 > 2

Note: *Results are presented as means (SD). Values in bold are significant.*

Overall, the data analysis revealed that individuals who maintain successful abstinence from 30 to 365 days are characterized by poorer decision-making, suggesting that they are more likely to make risky and disadvantageous decisions in both ambiguous situations which involve uncertain risk (IGT) and in situations with explicit risk contingencies (CGT). On the other hand, opiate users in long-term abstinence showed neither poorer (lack of performance differences with the control group) nor better (lack of performance differences with opiate users in short-term abstinence) decision-making on both neurocognitive tasks. These findings placed the decision-making capacities of opiate users in long-term abstinence in an intermediate position between the control group and the group of opiate users in short-term abstinence - their performance was comparable to that of control participants but not qualitatively different from that of opiate users in short-term abstinence. In addition, regardless of length of abstinence, both groups of opiate dependent participants reported a marked preference for smaller but immediate rewards and a tendency to neglect larger delayed rewards.

Personality and psychiatric domains of impulsivity

In terms of personality and psychiatric domains of *impulsivity*, our findings revealed that the three study groups differed significantly in levels of *psychopathy* [$H_{(2)} = 103.55$, $p < .001$, $\varepsilon^2 = .587$] and *trait impulsivity* [$F_{(2,177)} = 21.68$, $p < .001$, $\eta_p^2 = .197$]. Post-hoc analyses showed that the control group was characterized by lower levels of *psychopathy* and *trait impulsivity* compared to the two groups of opiate users ($p < .001$),

between which no significant differences were observed (p > .05). **Table 2** provides the descriptive statistics and group differences in measures of *psychopathy* and *trait impulsivity*.

Table 2. Group differences in measures of psychopathy and trait impulsivity.

	Controls (1)	**Short-term abstinence (2)**	**Long-term abstinence (3)**	***p***	**Contrast**
N	68	42	65		
PCL:SV Total score	2.75 (3.13)	13.40 (5.25)	12.32 (4.77)	**< .001**	1 < 2, 3
N	68	44	68		
UPPS Total score	84.93 (14.66)	102.66 (13.86)	96.50 (15.11)	**< .001**	1 < 2, 3

Note: *Results are presented as means (SD). Values in bold are significant.*

Our findings revealed that both groups of opiate users were characterized by elevated *psychopathy* and *trait impulsivity* compared to the control group. These results suggest that opiate users tend to react impulsively in a wide range of situations, have difficulties in following long-term plans consistently and often act without regard to the negative consequences of their actions. Opiate dependent participants were also characterized by increased *psychopathy* reflecting both deficits in interpersonal and affective functioning (e.g., manipulativeness, grandiosity, lack of empathy and remorse) and impulsive and antisocial lifestyle (e.g., impulsivity, irresponsibility, antisocial behaviors). The lack of significant differences between the two groups of opiate users suggests that *psychopathy* and *impulsivity* are stable personality features of opiate dependent individuals that persist even after a prolonged period of abstinence.

Impulsive actions

Our findings revealed that the three study groups differed significantly in their ability to successfully inhibit a dominant behavioral response on tasks measuring *action restraint* or *automatic inhibition* (*GNG False alarms* [$H_{(2)} = 8.36$, $p = .015$; $\varepsilon^2 = .048$]). Post hoc analyses showed that the control group was characterized by better automatic response inhibition compared to the two groups of opiate users ($p < .05$), between which no significant differences were observed ($p > .05$). In addition, no differences were found between the three study groups in their ability to cancel an already initiated motor response on tasks measuring *action cancellation* or *controlled inhibition* (*SST 150ms Inhibition* [$H_{(2)} = .047$, $p = .792$] and *SST 150ms*

Reaction Time (ms) [$H_{(2)}$ = .98, p = .612]). **Table 3** provides the descriptive statistics and group differences in indices of *impulsive action*.

Table 3. Group differences in indices of impulsive action.

	Controls (1)	**Short-term abstinence (2)**	**Long-term abstinence (3)**	***p***	**Contrast**
N	65	42	65	-	
GNG False alarms	12.82 (7.54)	17.98 (13.19)	15.71 (7.63)	**.015**	1 < 2, 3
N	67	44	67	-	
SST 150ms Inhibition	72.76 (23.18)	71.93 (19.51)	74.40 (18.12)	.792	-
SST 150 ms Reaction time	201 (71)	206 (68)	208 (69)	.612	-

Note: *Results are presented as means (SD). Values in bold are significant.*

In summary, our findings suggest that there are both specific deficits and intact functions in the distinct components of the *impulsive action* domain among abstinent opiate users. Our main results revealed that, regardless of length of abstinence, opiate dependent individuals were characterized by poorer *automatic inhibition*, as assessed by the GNG task, compared to the control group. Additional analyses, provided in **Appendix 5**, suggest that both groups of abstinent opiate users experienced difficulties in response inhibition and tended to respond prematurely when the task condition was of increased complexity and therefore required more cognitive resources. On the contrary, when the task condition was relatively easy, both groups of opiate dependent individuals showed performance similar to that of control participants. On the other hand, our findings revealed that response inhibition and reaction time, as assessed by the SST task measuring *controlled inhibition*, were similar across all study groups. Overall, our results suggest that impairments in *impulsive action* across opiate dependent individuals are specifically associated with a tendency toward premature reactions and a reduced ability to successfully inhibit a dominant behavioral response in more complex and cognitively demanding conditions, but not with impairments in the ability to cancel an already initiated motor response or to inhibit reactions in relatively easy task conditions.

Negative affectivity

Our results showed that the three groups differed significantly in *depression* [$H_{(2)}$ = 38.30, p < .0001, ε^2 = .213], *trait anxiety* [$H_{(2)}$ = 14.28, p = .001, ε^2 = . 079], *state anxiety* [$H_{(2)}$ = 15.98, p < .0001, ε^2 = .089], and *alexithymia* [$F_{(2,100)}$ = 4.33, p = .016, η_p^2 = .080], but not in *anxiety sensitivity* [$H_{(2)}$ = 4.99, p = .083]. **Table 4** presents descriptive statistics and group differences in measures of *negative affectivity*.

Table 4. Group differences in measures of negative affectivity.

	Controls (1)	Short-term abstinence (2)	Long-term abstinence (3)	*p*	Contrast
N	68	44	68	-	
Depression	3.43 (4.06)	8.93 (5.83)	7.74 (6.19)	**< .001**	1 < 2, 3
N	68	43	68	-	
Trait anxiety	34.54 (8.79)	39.28 (9.65)	41.10 (10.34)	**.001**	1 < 3
State anxiety	30.38 (7.30)	35.74 (8.26)	35.19 (9.46)	**< .001**	1 < 2, 3
N	68	45	68	-	
Anxiety sensitivity	15.04 (7.69)	18.89 (10.17)	17.57 (7.67)	.083	-
N	44	19	40	-	
Alexithymia	42.48 (8.08)	49.05 (9.89)	46.75 (9.51)	**.016**	1 < 2

Note: *Results are presented as means (SD). Values in bold are significant.*

Post hoc analyses showed that participants in the control group scored significantly lower on *depression* and *state anxiety* compared to participants from both groups of opiate users (p < .001). Opiate users in long-term abstinence reported elevated *trait anxiety* (p < .01) compared to the control group, whereas *alexithymia* was elevated only in the group of opiate users in short-term abstinence (p < .05). There were no significant differences in dimensions of *negative affectivity* between the two groups of abstinent opiate users.

Our findings suggest that increased *depression* and elevated *state anxiety* are common features of opiate dependent individuals in both short-term and long-term abstinence. On the other hand, our results suggest that *trait anxiety* is a specific characteristic of opiate dependent individuals in long-term

abstinence, whereas difficulties in identifying and describing emotions (i.e., *alexithymia*) are more strongly related to the short-term protracted abstinence stage of opiate addiction.

Objective 2

Impulsivity

To examine the effects of length of abstinence on distinct dimensions of *impulsivity*, we conducted a series of hierarchical multiple regressions. All regression analyses controlled for the effects of other relevant covariates and followed the same steps: Step 1 included the demographic variables: *biological sex*, *age*, and *fluid intelligence* (Raven's estimated IQ). Step 2 added the variables relevant to opiate use: *duration of opiate dependence* (in days) and *severity of opiate dependence* (number of DSM-IV opiate dependence symptoms met). Step 3 included the *length of abstinence* (in days).

Impulsive choice

We conducted three separate hierarchical multiple regressions with distinct indices of *impulsive choice* domain as dependent variables: 1) decision-making under ambiguity (*IGT Block 3, 4, 5*); 2) decision-making under risk (*CGT Quality of decision-making*); 3) temporal reward discounting (*MCQ Overall k*). Data from each regression analysis is presented in a separate section.

Decision-making under ambiguity

The model in Step 1 was significant [$F_{(3,103)} = 4.54$, $p = .005$; $R^2_{adjusted} = .091$], explaining 9.1% of the variance in the performance on *IGT Block 3, 4, 5* index. The only significant predictor was *fluid intelligence* (ß = .322, $p = .001$), with higher IQ values being associated with better decision-making under ambiguity. Step 2 [$F_{(5,101)} = 2.75$, $p = .023$; $R^2_{adjusted} = .076$] was also significant, but the change in R^2 did not reach the required level of significance. Step 3 [$F_{(6,100)} = 3.04$, $p = .009$; $R^2_{adjusted} = .103$] was significant, indicating a significant change in R^2. *Fluid intelligence* (ß = .325, $p = .001$) and length of abstinence (ß = .205, $p = .047$) were identified as the main predictors in the model, with longer periods of abstinence being associated with improved performance on the IGT task. The overall model explained a total of 10.3% of the variance in the quality of decision-making under ambiguity.

Decision-making under risk

Neither Step 1 [$F_{(3,105)} = 1.07$, $p = .366$; $R^2_{adjusted} = .002$] nor Step 2 [$F_{(5,103)} = 2.16$, $p = .068$; $R^2_{adjusted} = .051$] were significant. The model in Step 3 was significant [$F_{(6,104)} = 3.29$, $p = .005$; $R^2_{adjusted} = .113$]. The inclusion of length of abstinence resulted in a significant change in R^2. Longer periods of abstinence (ß = .285, p =

.005) and more opiate dependence symptoms (ß = .256, p = .008) were associated with improved decision-making quality. The overall model explained a total of 11.3% of the variance in the *CGT Quality of decision-making* index.

Temporal reward discounting

The models in Step 1 [$F_{(3,98)} = 2.27$, $p = .085$; $R^2_{adjusted} = .036$], Step 2 [$F_{(5,96)} = 1.45$, $p = .214$; $R^2_{adjusted} = .022$], and Step 3 [$F_{(6,95)} = 1.20$, $p = .305$; $R^2_{adjusted} = .012$] were not significant. The only significant predictor was *fluid intelligence* (ß = -.257, p = .013), with higher IQ values being associated with reduced delay discounting.

Impulsive action

Data from regression analyses with the two main *impulsive action* task indices as dependent variables are presented in separate sections: 1) action restraint (*GNG False alarms*) and 2) action cancellation (*SST 150ms Inhibition*).

Action restraint (automatic inhibition)

Step 1 was significant [$F_{(3,100)} = 5.64$, $p = .001$; $R^2_{adjusted} = .119$], explaining 11.9% of the variance in the *GNG False alarms*. The only significant predictor was *fluid intelligence* (ß = -.374, $p < .001$), with higher IQ values being associated with increased response inhibition. The models in Step 2 [$F_{(5,98)} = 3.60$, $p = .005$; $R^2_{adjusted} = .112$] and Step 3 [$F_{(6,97)} = 2.98$, $p = .010$; $R^2_{adjusted} = .103$] were also significant, but the change in R^2 did not reach the required level of significance ($p > .05$). *Fluid intelligence* remained the only significant predictor in the model.

Action cancellation (controlled inhibition)

Models in Step 1 [$F_{(3,104)} = 1.23$, $p = .301$; $R^2_{adjusted} = .007$], Step 2 [$F_{(5,102)} = 0.83$, $p = .533$; $R^2_{adjusted} = -.008$], and Step 3 [$F_{(6,101)} = 0.79$, $p = .581$; $R^2_{adjusted} = -.012$] were not significant. There were no significant predictors of the ability to cancel an already initiated motor response.

Personality and psychiatric aspects of impulsivity

We conducted two separate hierarchical multiple regression analyses, with *psychopathy* (*PCL:SV Total score*) and *trait impulsivity* (UPPS *Total score*) total scores as dependent variables. Data from each regression analysis is presented in a separate section.

Psychopathy

Step 1 was significant [$F_{(3,103)}$ = 12.74, p = .000; $R^2_{adjusted}$ = .249], explaining 24.9% of the variance in *psychopathy*. Male gender (ß = -.457, p < .001) and lower *fluid intelligence* (ß = -.192, p = .027) were associated with increased *psychopathy*. Step 2 [$F_{(5,101)}$ = 8.52, p = .000; $R^2_{adjusted}$ = .262] and Step 3 [$F_{(6,100)}$ = 7.29, p = .000; $R^2_{adjusted}$ = .263] were significant, but the change in R^2 did not reach the required level of significance (p > .05). *Fluid intelligence* and male gender remained the only significant predictors in the model explaining 26.3% of the variance in *psychopathy*.

Trait impulsivity

The models in Step 1 [$F_{(3,107)}$ = 1.27, p = .288; $R^2_{adjusted}$ = .007] and Step 2 [$F_{(5,105)}$ = 0.80, p = .549; $R^2_{adjusted}$ = -.009] were not significant. After the inclusion of length of abstinence in the model, Step 3 [$F_{(6,104)}$ = 2.57, p = .023; $R^2_{adjusted}$ = .079] reached significance, with the overall model explaining 7.9% of the variance in *trait impulsivity*. The only significant predictor was length of abstinence (ß = -.336, p = .001), with longer periods of abstinence being associated with lower *trait impulsivity*.

Negative affectivity

To examine the effects of length of abstinence on the domain of *negative affectivity*, we conducted a series of hierarchical multiple regression analyses which also controlled for the effects of other relevant covariates. All regression analyses followed the same steps: Step 1 included the demographic variables: *biological sex* and *age*. Step 2 added the variables relevant to opiate use: *duration of opiate dependence* (in days) and *severity of opiate dependence* (number of DSM-IV opiate dependence symptoms met). Step 3 included the *length of abstinence* (in days).

Data from the regression analyses for the *negative affectivity* indices assessing *depression* (*BDI-II Total score*) and *state anxiety* (*STAI-Y-S Total score*) are presented in separate sections.

Depression

The models in Step 1 [$F_{(2,108)}$ = 2.87, p = .061; $R^2_{adjusted}$ = .033] and Step 2 [$F_{(4,106)}$ = 1.93, p = .112; $R^2_{adjusted}$ = .033] were not significant, with the model in Step 3 [$F_{(5,105)}$ = 2.30, p = .050; $R^2_{adjusted}$ = .056] approaching significance. *Age* was positively related to *depression* (ß = .255, p = .034). In addition, length of abstinence was identified as a marginally significant predictor (ß = -.193, p = .060), suggesting that there is a trend for *depression* levels to decrease with increases in periods of abstinence.

State anxiety

The model in Step 1 [$F_{(2,107)}$ = 3.81, p = .025; $R^2_{adjusted}$ = .049] was significant, with *female gender* being associated with elevated *state anxiety* (ß = .262, p = .007). Step 2 [$F_{(4,105)}$ = 1.90, p = .116; $R^2_{adjusted}$ = .032] was not significant, but when length of abstinence was added in Step 3 [$F_{(5,104)}$ = 2.63, p = .028; $R^2_{adjusted}$ = .070] the model became significant, reflecting a significant change in R^2 (p < .05). *Female gender* (ß = .314, p = .002) and length of abstinence (ß = -.233, p = .024) were identified as significant predictors of *state anxiety*.

DISCUSSION

Effects of length of abstinence on impulsive choice

One of the major assumptions associated with the main findings of the current study was that the tendency toward temporal reward discounting (MCQ) remained relatively stable even in periods of long-term abstinence and was not significantly affected by length of abstinence. This data suggests that, regardless of the period of abstinence, opiate users tend to neglect future delayed rewards and manifest increased sensitivity to immediate rewards, even though immediate rewards represent disadvantageous decision-making strategy in the long term. It is important to emphasize that our results cannot be adequately interpreted in terms of potential recovery or lack of recovery of function due to the main limitations associated with the cross-sectional design employed in the current study. For this reason, future studies would benefit from longitudinal designs to examine the trajectory of potential changes in delay discounting with increasing periods of abstinence. Such studies may have important practical implications for the treatment and rehabilitation of opiate dependence due to the high predictive validity of delay discounting in relation to the risk of relapse (Turner et al., 2021).

In addition, our data suggests that opiate users in short-term abstinence are characterized by disadvantageous decision-making under both explicit risk conditions when the contingencies of the decision options are explicitly provided (CGT) and ambiguous risk conditions when the probabilities of the decision outcomes are unknown (IGT). These results are consistent with previous research findings and support the assumption that decision-making remain significantly impaired within the first year of abstinence following chronic opiate use (Kriegler et al., 2019; Li et al., 2013; Tolomeo et al., 2016; Zhang et al., 2011). Contrary to our initial hypotheses, we did not register any group differences in decision-making under risk and ambiguity between the control group and the group of opiate users in long-term abstinence. Although these results may imply that optimal decision-making abilities are likely to be

restored in the course of long-term abstinence, regression analyses identified very small effects of length of abstinence on the individual performance on decision-making tasks. Therefore, it appears that length of abstinence is not a major factor affecting decision-making processes among opiate users. As performance on *impulsive choice* tasks is determined by a number of additional lower-order factors and involves multiple subtle processes and mechanisms such as fluid intelligence, inhibitory control, working memory, while also engaging emotional processes (see Rochat et al., 2019), future research is needed to assess the relative involvement of these mechanisms in the quality of decision-making and temporal reward discounting in individuals dependent to different classes of psychoactive substances. Findings from such studies could provide additional information related to the interaction effects between excessive and chronic substance use, the period of abstinence, and other cognitive functions underlying or mediating disadvantageous decision-making.

In summary, the results of the current study suggest that if there is a relationship between length of abstinence and changes in *impulsive choice* domain, it is most likely a weak one. One potential explanation of our findings can be based on the main assumptions of previous neuroimaging studies conducted in samples of substance dependent individuals that reported persistent impairments in the structure and function of the orbitofrontal cortex which is significantly involved in *impulsive choice* (Lyoo et al., 2006; Tanabe et. Al., 2009; Volkow & Fowler, 2002). These studies suggested that prolonged exposure to the toxicological effects of various psychoactive substances (including opiates) leads to alterations in brain functioning which may underlie the maladaptive behaviors and disadvantageous decisions that characterize the daily lives of people suffering from substance use disorders. However, contrary to this hypothesis, impaired decision-making and increased temporal reward discounting can be regarded as risk factors that precede the onset of substance dependence and may explain the dramatic tendency of people with addictions to continue their drug use despite the negative long-term consequences. In this context, the marginal “improvement” in decision-making among opiate users in long-term abstinence observed in the present study may not be due to the effects of length of abstinence, but may rather reflect stable features of the premorbid cognitive functioning of people suffering from addictions. In light of these assumptions, it seems possible that opiate users in successful long-term recovery are characterized by more preserved decision-making functions at baseline, which in turn may explain their ability to successfully maintain extended periods of abstinence. It is important to emphasize that the specifics of the research design employed in the current study and the main methodological limitations detected in previous studies in the field hinder the identification of the actual underlying mechanisms involved in the increased *impulsive choice* of individuals diagnosed with opiate dependence. The potential persistent

impairments in the *impulsive choice* domain require longitudinal studies that could adequately address questions related to the mechanisms underlying disadvantageous decision-making in opiate users – are decision-making impairments recovering with abstinence or rather represent a stable cognitive feature that is not particularly affected by the period of abstinence.

Effects of length of abstinence on impulsive action

Our main findings related to the domain of *impulsive action* suggested that regardless of the period of sustained abstinence, opiate users are characterized by diminished ability to inhibit a prepotent motor response (i.e., *automatic inhibition*) as measured by the GNG task. It is possible that these findings reflect task specific effects. In contrast to previous studies (Morie et al., 2014; Verdejo-Garcia et al., 2007b; Yang et al., 2009) that used relatively easy Go/No-Go paradigms, the task implemented in the current study included No-Go conditions of varying difficulty. The additional analyses supported this hypothesis by revealing that the main difference between abstinent opiate users and control participants was observed only in the "hard" No-Go trials. These findings suggest that when the task was more cognitively demanding, opiate users showed impaired performance compared to the control group, but when the task condition was relatively easy, response inhibition appears to be intact. It is important to note that the effects of these differences were moderate, suggesting that length of abstinence (short-term and long-term abstinence) was not a key factor affecting the performance on tasks measuring *automatic inhibition*. Thus, future research is needed to investigate the effects of other relevant lower-order factors (e.g., emotional processes, attention, memory) that might influence *automatic inhibition* in the context of opiate dependence by additionally examining their interaction effects with length of abstinence.

On the other hand, the lack of group differences in the performance on the SST task suggests that *controlled inhibition* is not significantly impaired in opiate users, supporting the main findings of the only study in the field (Ahn & Vassileva, 2016) that applied the same Stop Signal paradigm to assess *impulsive action* in opiate dependence. As the majority of previous studies on response inhibition implemented GNG paradigms, our knowledge about the quality of *controlled inhibition* in opiate users is limited and requires further investigation in different samples of opiate dependent individuals.

The variations in performance on distinct *impulsive action* tasks detected in the current study may be due to the long-term toxicological effects of opiates on the different neural circuits mediating the individual performance on Stop Signal and Go/No-Go paradigms. On the other hand, both types of response inhibition may be significantly impaired among opiate users, but the ability to cancel an already initiated

response may recover earlier in the course of abstinence. In this context, the relatively long periods of abstinence maintained by our opiate dependent participants may explain the lack of group differences observed in performance on the *controlled inhibition* task. To address the gaps in the literature, future research could additionally examine different types of response inhibition in active and abstinent opiate users. In addition, the implementation of longitudinal designs and neuroimaging approaches could significantly improve our knowledge about different types of response inhibition in opiate dependence.

In summary, based on our main findings we can speculate that opiate dependence is associated with long-term impairments in *automatic inhibition* involving *action restraint*, but not with the more *controlled inhibition* processes that engage *action cancellation*. In addition, length of abstinence may have no significant effect on response inhibition, with poorer *automatic inhibition* persisting into the longer-term stages of abstinence following chronic opiate use. If supported by future research, these findings may have important practical implications in the treatment and rehabilitation of opiate dependence.

Effects of length of abstinence on personality and psychiatric dimensions of impulsivity

Our findings are consistent with previous studies that reported increased *trait impulsivity* (Dissabandara et al., 2014; Ghosh et al., 2019; Yang et al., 2021) and *psychopathy* (Ahn & Vassileva, 2016; Vassileva et al., 2019; Psederska et al., 2019; 2021) among individuals with opiate dependence. These findings suggest that, regardless of the period of abstinence, opiate users tend to react impulsively in a wide range of situations and are characterized by pronounced interpersonal-affective (e.g., manipulativeness, lack of remorse and empathy) and impulsive-antisocial (e.g., irresponsibility, lack of long-term goals, antisocial behaviors) *psychopathy* features.

A surprising finding was that length of abstinence predicted lower *trait impulsivity* in former opiate users. The UPPS was designed to measure long-term and pervasive impulsive behavioral patterns that remain relatively stable over time and therefore, it is unlikely that levels of *trait impulsivity* decline with abstinence. Therefore, these findings can be interpreted in terms of the individual specifics of people who are able to maintain effective and successful long-term abstinence. From this perspective, we can hypothesize that lower *trait impulsivity* is a specific premorbid characteristic of individuals who recover successfully from chronic opiate use and are able to maintain long periods of abstinence. Several studies support this hypothesis by reporting that lower *trait impulsivity* at baseline is predictive of increased treatment effectiveness and lower dropout rates (Mallorquí-Bagué et al., 2018; Patkar et al., 2004; Staiger et al., 2014; Winhusen et al., 2013). Future longitudinal studies can assess *trait impulsivity* across different

stages of recovery (e.g., prior to treatment as well as at different stages of abstinence) to further clarify its role in protracted abstinence, one of the least well-understood stages of the addiction cycle.

On the other hand, there were no group differences in *psychopathy* between opiate users in short-term and long-term abstinence, and length of abstinence had no effects on *psychopathy*. These findings suggest that *psychopathy* can be considered a relatively stable personality feature of individuals who are particularly vulnerable to develop chronic opiate use. Given that *psychopathy* was identified as the highest and the only common predictor of dependence on different classes of drugs (Ahn & Vassileva, 2016; Vassileva et al., 2019), more detailed investigation of its effects on neurocognitive functioning of individuals diagnosed with addictions is needed.

Effects of length of abstinence on negative affectivity

Our main findings related to the *negative affectivity* domain were that regardless of length of abstinence, opiate users were characterized by increased *depression* and *state anxiety* compared to control participants. In addition, *alexithymia* was elevated only in opiate users in short-term abstinence, whereas *trait anxiety* was pronounced only in opiate users in long-term abstinence.

Our results suggest that opiate users are more vulnerable to experiencing heightened *anxiety* and *depression* and these negative emotional states persist in both stages of short-term and long-term abstinence. On the other hand, individuals who manage to maintain longer periods of abstinence were characterized by increased *trait anxiety*. However, there were no specific effects of length of abstinence (short-term vs. long-term) on *trait anxiety*, which suggests that individuals who maintain long-term abstinence do not differ significantly in terms of *trait anxiety* from those who maintain shorter periods of abstinence. Thus, *trait anxiety* may not be particularly relevant to the process of recovery from chronic opiate use, and may rather reflect a specific personality disposition that increases the risk of initial drug use (Ersche et al., 2012). In addition, our results suggest that difficulties in identifying and describing emotions (i.e., *alexithymia*) are more pronounced within the first year of abstinence. These findings support the idea that *alexithymia* can be considered a state phenomenon, rather than stable personality feature, which is based on previous studies that reported significant reduction in its levels in the course of treatment (de Haan et al., 2012). Although this hypothesis sounds plausible, it should be emphasized that fewer participants in short-term abstinence were rated on the TAS-20 scale due to its later inclusion in the study protocol. Therefore, it is difficult to draw valid conclusions regarding group differences in *alexithymia*, which may also be influenced by sample size. Future studies that include larger samples or

implement longitudinal designs may further test these hypotheses by examining possible changes in *alexithymia* across different periods of abstinence.

In summary, our results suggest that *negative affectivity* may persist not only within the first year of abstinence, but in the longer-term stages of protracted abstinence. However, it is important to emphasize that the effect sizes of group differences in *state anxiety*, *trait anxiety*, and *alexithymia* were moderate, suggesting that length of abstinence was not the primary factor influencing individual differences in *negative affectivity*. Therefore, it is possible that additional factors, which were not controlled for in the current study, possess greater explanatory power for variations in distinct domains of *negative affectivity*. For example, coping strategies, individual vulnerability to environmental stressors (Dermody et al., 2013; Zeidner & Ben-Zur, 2014), resilience (Smith et al., 2016), self-efficacy, and social support (Wang et al., 2022) may exert additional effects on the individual vulnerability to experiencing negative emotions or at least moderate the effects of opiate use and length of abstinence on *negative affectivity*. Future research is needed to further investigate the effects of such potential moderators of negative affect in substance use disorders. Increased precision and detection of more subtle, individual-specific pathways leading to exacerbated negative affect could support the identification of subgroups of patients who are specifically vulnerable to negative emotional states and could be enrolled in more personalized interventions aimed at negative affect reduction by addressing various individual and environmental risk factors.

Practical implications

The implementation of a rich research battery to examining distinct dimensions of *impulsivity* and *negative affectivity* has inspired hypotheses about the underlying profiles of impairments and resources that seemed to have both common and unique characteristics in opiate users in short-term and long-term abstinence. Based on our findings, we can suggest that, regardless of the period of abstinence, opiate users are characterized by increased temporal reward discounting, impaired *automatic inhibition* and elevated levels of *psychopathy*, *trait impulsivity*, *depression* and *state anxiety*. In addition, opiate dependent individuals in short-term abstinence are uniquely characterized by disadvantageous decision-making under risk and ambiguity and elevated *alexithymia*. On the other hand, opiate users in long-term abstinence are uniquely characterized by increased *trait anxiety*. In addition, there was a trend towards improved decision-making, reduced *trait impulsivity* and *negative affectivity* (i.e., *state anxiety* and *depression*) with increasing periods of abstinence. It is important to emphasize that the proposed profiles of deficits and resources are strictly speculative. Therefore, it is important that future studies implementing machine-learning approaches additionally test the accuracy of these behavioral markers in

differentiating opiate users based on length of abstinence. Potential support of these findings in conjunction with the identification of additional personality, behavioral, cognitive, and neurobiological markers may have key implications for the treatment and rehabilitation of opiate dependence.

Our results are consistent with previous studies suggesting that some deficits in cognitive and affective functioning are long-term and not significantly affected by length of abstinence, meaning that they may exert their negative effects even after years of abstinence. Overall, these findings require increased therapeutic attention and development of novel personalized interventions tailored to the individual vulnerability profiles of people in protracted abstinence.

First, a relatively brief screening battery need to be developed including the assessment of various personality, neurocognitive and affective dimensions that are either often impaired in opiate users or are considered premorbid risk factors for developing opiate dependence. The implementation of a standardized research battery may reveal more precise individual profiles reflecting key areas of impairments and resources based on individual performance. The ability to identify distinct subgroups of individuals who represent distinct vulnerability profiles would support the development of more precise individualized interventions that have the potential to increase the effectiveness of opiate dependence treatment while significantly reducing the risks associated with the relapsing nature of the disorder.

A variety of therapeutic programs are currently being developed that could effectively address distinct *impulsivity* and *negative affectivity* dimensions in individuals in recovery from severe opiate addiction. Examples of such interventions include:

- The *Goal Management Training* (GMT; Levine et al., 2000, 2011) includes various interventions aimed at improving different cognitive processes and functions. The program consists of multiple sessions targeting working memory, goal identification and goal monitoring, response inhibition, mindfulness, and decision-making (Levine et al., 2001). The primary aim of the program is to train patients to employ various goal-oriented approaches to guide their behavior. For example, patients are trained to stop ongoing behavior and reflect on their current emotions, behaviors and goals before making complex decisions (Levine et al., 2001). Evidence from the small number of studies evaluating the effectiveness of GMT in samples of substance dependent individuals produced optimistic results (Alfonso et al., 2011; Valls-Serrano et al., 2016).
- The *Mindfulness-Oriented Recovery Enhancement* (MORE; Garland et al., 2010) program is among the most promising contemporary interventions, incorporating a wide variety of techniques that

support patients in regulating different emotional states through breathing practices, meditation, and various exercises that link the basic mindfulness principles to various addiction-specific risk behaviors (e.g., relapse, craving, etc.) (Garland et al., 2010). Several studies have documented the effectiveness of mindfulness-based interventions on improving emotion regulation and decreasing negative affectivity (see Schumer et al., 2018 and Tang et al, 2016). In addition, these studies revealed that consistent engagement in mindfulness can foster neuroplasticity in brain regions mediating various functions associated with the quality of cognitive processes and emotion regulation (Hölzel et al., 2011; see Tang et al., 2015 and Tang et al., 2016).

- Paradigms involving *episodic future thinking* are among the most reliable methods for reducing temporal reward discounting in laboratory settings (see Bickel & Athamneh, 2020; Mellis et al., 2019; Stein et al., 2016). These paradigms ask participants to imagine and relive in fantasy the future outcomes of various decisions they make in the present. Due to the effectiveness of episodic future thinking-based approaches in reducing temporal reward discounting (Mellis et al., 2019; Snider et al., 2016; Sofis et al., 2020) and alcohol use (Snider et al., 2016), clinical interventions engaging episodic future thinking are currently being developed and tested for clinical purposes (Lu et al., 2018).
- The *Preventure* program (Conrod, 2016) is among the most encouraging examples of personality-based prevention approach for substance use disorders. The program incorporates a combination of psychoeducation, modified cognitive-behavioral techniques, and motivational interviewing to work with subgroups of vulnerable adolescents who fall into one of the four core personality risk profiles (i.e., impulsivity, sensation seeking, anxiety sensitivity, and hopelessness) associated with increased susceptibility to problematic substance use. The high effectiveness of *Preventure* (Conrod et al., 2013) can inspire the development of novel personality-based interventions targeting active substance users and people in recovery.

In summary, the combination of current findings and prior research have supported the increased need for the development of novel personalized rehabilitation programs targeting former opiate users in long-term abstinence. We propose that a combination of personality-informed treatment programs and neurocognitive-based techniques including interventions targeting goal management, episodic future thinking, response inhibition, and mindfulness, could assist the recovery process in the protracted abstinence stage and may support the improvement of some of the most pervasive and persistent cognitive and affective impairments observed among abstinent opiate users. The development of tailored modular interventions targeting deficits in cognitive functioning and emotion regulation may have broad

practical implications for opiate dependence rehabilitation and can further address the main limitations of traditional therapeutic alternatives.

Strengths and limitations

The current study has several key methodological strengths aimed at addressing the limitations of prior research in the field:

- The study examined distinct dimensions of *impulsivity* and *negative affectivity* in opiate dependence, which is rather understudied in addiction literature. In addition, the current study design aimed to address the limitations of the small number of previous studies that failed to control for the confounding effects of polysubstance dependence on distinct dimensions of *impulsivity* and *negative affectivity* in opiate users.
- The current study examined distinct *impulsivity* and *negative affectivity* dimensions in protracted abstinence, one of the least well-understood stages of the addiction cycle. The study examined similarities and differences in neurocognitive and affective functioning among former opiate users in different stages of protracted abstinence – short-term abstinence [< 12 months] and long-term abstinence [> 12 months].
- The study utilized a rich research battery to provide the parallel assessment of distinct dimensions of *impulsivity* and *negative affectivity* in opiate addiction and in different stages of protracted abstinence. This research strategy reflects our attempt to address one of the major limitations of prior studies, which are focused primarily on the unidimensional measurement of both *impulsivity* and *negative affectivity* and failed to provide a comprehensive assessment of their distinct dimensions.

Despite these advantages, the current study has several limitations that need to be considered:

- The study utilized only behavioral assessments of *impulsivity* and *negative affectivity*, and does not include genetic and neuroimaging approaches.
- An additional limitation was that the study examined two of the three key neurofunctional domains implicated in addictions, failing to capture the domain of *incentive salience*.
- The study did not include the assessment of other core cognitive functions that are significantly impaired due to chronic and severe opiate use (e.g., working memory, compulsivity).
- One of the major weaknesses of the thesis is related to the extreme reliance on self-report measures for capturing the *negative affectivity* domain.

- In addition, the current study employed a cross-sectional design, which significantly limits our conclusions about the effects of length of abstinence on distinct dimensions of *impulsivity* and *negative affectivity*.

CONCLUSION

Our main findings suggest that some impairments in cognitive and affective functioning can be observed even among individuals who successfully maintain long-term abstinence following chronic opiate use. Deficits in decision-making (i.e., temporal reward discounting) and response inhibition, as well as increased negative affect and *trait impulsivity* persist not only within the first year of abstinence, but are also pronounced in the longer-term stages of protracted abstinence. These findings emphasized the increasing need for developing novel modular interventions that are more personalized and sensitive to the individual needs of people in successful recovery from prolonged and severe opiate addiction. The development of individualized rehabilitation programs targeting persistent impairments in neurocognitive and emotional functioning could support recovery and assist the decrease of various dysfunctional behaviors associated with problems in important life areas of individuals who seek recovery.

Summary of contributions

(1) The present study established specific impairments in distinct dimensions of *impulsive choice* among former opiate users in different stages of protracted abstinence:

- Former opiate users in short-term abstinence [< 12 months] are characterized by impairments in decision-making under risk and ambiguity, reflecting reliance on risky and disadvantageous decision-making strategies.
- Former opiate users in both short-term [< 12 months] and long-term [> 12 months] abstinence are characterized by an increased temporal reward discounting associated with pronounced preference for immediate over delayed rewards.

(2) The current study established variations in the performance of abstinent opiate users on different types of response inhibition tasks reflecting distinct *impulsive action* domains:

- Former opiate users in both short-term [< 12 months] and long-term [> 12 months] abstinence were characterized by premature behavioral reactions and difficulties in *automatic inhibition*, reflecting the individual ability to inhibit dominant reactions in cognitively demanding conditions.
- Former opiate users in both short-term [< 12 months] and long-term [> 12 months] abstinence were characterized by intact *controlled inhibition*, reflecting the individual ability to cancel an already initiated motor response.

(3) The present study established both common and specific profiles of impairments in dimensions of *negative affectivity* among former opiate users in different stages of protracted abstinence:

- Increased *depression* and elevated *state anxiety* characterized both groups of former abstinent users, suggesting that these dimensions of *negative affectivity* are common to opiate dependent individuals in protracted abstinence.
- Increased *trait anxiety* was specific to former opiate users in long-term abstinence [>12 months].
- Increased *alexithymia* was specific to former opiate users in short-term abstinence [<12 months].
- *Anxiety sensitivity* did not emerge as a significant discriminative feature of the protracted stage of opiate addiction.

(4) The current study established variations in the effects of length of abstinence on distinct dimensions of *impulsivity* and *negative affectivity*. Our results suggested that length of abstinence may affect only

some dimensions of *impulsivity* and *negative affectivity*, while exerting no impact on other components of these neurofunctional domains:

- Decision-making under risk and ambiguity was affected by length of abstinence, with longer periods of abstinence being associated with improved quality of decision-making.
- Length of abstinence had effects on *trait impulsivity* and *state anxiety*, with longer periods of abstinence being associated with reductions in *trait impulsivity* and *state anxiety*.
- It is important to note that we did not detect effects of length of abstinence on: 1) temporal reward discounting; 2) *impulsive action* domain; 3) *psychopathy*; and 4) *depression*, *trait anxiety*, *alexithymia*, and *anxiety sensitivity*, suggesting that these components of *impulsivity* and *negative affectivity* are not significantly affected by length of abstinence.

(5) Based on the current findings, we provided ideas for future research in the field and discussed the clinical implications of these findings in the treatment and rehabilitation of opiate addiction.

Author's Publications

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