Advances in Mental Health and Addiction
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Michela Balconi
Salvatore Campanella *Editors*

Advances in Substance and Behavioral Addiction

The Role of Executive Functions

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Over the past several decades we have witnessed dramatic shifts in prevailing approaches to mental health and addiction. Significant scientific achievements have led to novel treatment options that impacted the experiences of individuals with mental disorders. In recent years, new perspectives have begun to influence the way we address mental health and substance dependencies, resulting in a greater emphasis on mental health promotion and prevention strategies. Despite these progressions, mental health care systems too often remain stagnant, fragmented, and peripheral.

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The Role of Executive Functions

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To those who work with me every day.
Joys and hardships of today, with a look to the future

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Part I
The Executive Functions in "Old" and "New" Addictions

Chapter 1
Similarities and Differences Between "Old" and "New" Addictions: The Focus on Executive Functions and Reward Mechanisms

Michela Balconi

1.1 Definition of Different (Old and New) Addictions

According to the last version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V, American Psychiatric Association, 2013), a total of ten categories of drugs are listed in the Substance-Related Disorders: alcohol, caffeine, cannabis, hallucinogens, inhalants, opioids, sedatives, hypnotics, and anxiolytics, stimulants (amphetamine-type substances, cocaine, and other stimulants), tobacco, and other (or unknown) substances. In the DSM-V, this "family of disorders" includes both Substance Use Disorders (SUD) and Substance-Induced Disorders; regarding the latter, three main conditions are classified as induced by the substance: intoxication, withdrawal, and a comprehensive range of substance-induced mental disorders (American Psychiatric Association, 2013).

The excessive intake of all previously mentioned drugs directly stimulates the brain reward system, which is involved in behavioural reinforcement and memory production, and boosts it in a non-functional way, to the point that normal activities and adaptive behaviours can be neglected (Balconi et al., 2014a, c; Balconi & Finocchiaro, 2015).

Besides, predisposing factors also play an important role in this category of disorders, for which individuals with reduced levels of self-control (suggesting possible deficit in brain inhibitory control brain networks) may be especially

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predisposed to the development of SUD, meaning that for certain people, the origins of SUD may be seen in habits preceding the actual start of drug use.

In the DSM-V, SUD is essentially characterized by "a cluster of cognitive, behavioural, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems". The diagnosis of a SUD is based on a pathological pattern of behaviours related to the use of the substance, which includes four main areas: *impaired control*, *social impairment*, *risky use*, and *pharmacological criteria*. See below for the DSM-V's features and four diagnostic grouping criteria for all SUD:

Impaired control (Criteria 1–4):

1. The individual may take the substance in larger amounts or over a longer period than was originally intended.
2. The individual may express a persistent desire to cut down or regulate substance use and may report multiple unsuccessful efforts to decrease or discontinue use.
3. The individual may spend a great deal of time obtaining the substance, using the substance, or recovering from its effects. In some instances of more severe SUD, virtually all of the individual's daily activities revolve around the substance.
4. Craving is manifested by an intense desire or urge for the drug that may occur at any time, but is more likely when in an environment where the drug previously was obtained or used. Craving has also been shown to involve classical conditioning and is associated with the activation of specific reward structures in the brain. Craving is queried by asking if there has ever been a time when they had such strong urges to take the drug that they could not think of anything else. Current craving is often used as a treatment outcome measure because it may be a signal of impending relapse.

Social impairment (Criteria 5–7) includes relational problems or giving up on interpersonal problems:

5. Recurrent substance use may result in a failure to fulfil major role obligations at work, school, or home.
6. The individual may continue substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.
7. Important social, occupational, or recreational activities may be given up or reduced because of substance use. The individual may withdraw from family activities and hobbies in order to use the substance.

Risky use of the substance (Criteria 8 and 9):

8. This may take the form of recurrent substance use in situations in which it is physically hazardous.
9. The individual may continue substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance. The key issue in evaluating this

criterion is not the existence of the problem, but rather the individual's failure to abstain from using the substance despite the difficulty it is causing.

Pharmacological criteria are the final grouping (Criteria 10 and 11):

10. Tolerance is signalled by requiring a markedly increased dose of the substance to achieve the desired effect or a markedly reduced effect when the usual dose is consumed. The degree to which tolerance develops varies greatly across different individuals as well as across substances and may involve a variety of central nervous system effects. Tolerance may be difficult to determine by history alone, and laboratory tests may be helpful. It must also be distinguished from individual variability in the initial sensitivity to the effects of particular substances.
11. Withdrawal is a syndrome that occurs when blood or tissue concentrations of a substance decline in an individual who had maintained prolonged heavy use of the substance. After developing withdrawal symptoms, the individual is likely to consume the substance to relieve the symptoms. Withdrawal symptoms vary greatly across the classes of substances, and separate criteria sets for withdrawal are provided for the drug classes.

Neither tolerance nor withdrawal is necessary for a diagnosis of a substance use disorder. However, for most classes of substances, a past history of withdrawal is associated with a more severe clinical course (i.e., an earlier onset of a substance use disorder, higher levels of substance intake, and a greater number of substance-related problems).

In addition to the SUD, gambling disorder is also included in this section of the DSM-V manual, representing the evidence that gambling behaviour engages reward pathways comparable to those stimulated by addiction to drugs and generate some behavioural symptoms similar to SUD. It has been defined as a "Non-Substance-Related Disorder" sharing the features of risky use, social impairment, and sense of urgency with SUD. Specifically, according to DSM-V, gambling disorder entails:

– Risking and eventually losing something of value in the expectation that something of greater value can be obtained.
– A "loss tracking" pattern may develop, with an urgent need to keep playing (often by placing larger bets or taking greater risks) to undo a loss or series of losses.
– The persistent and chronic maladaptive gambling activity that disrupts personal, family, and/or vocational pursuits.

There are also some associated features supporting diagnosis for pathological gambling (PG) related to cognition, for which this disorder characterized by distortions in thinking (namely, superstition, denial, a sense of power and control over the outcomes of events of chance, overconfidence), but also impulsiveness, competitiveness, feeling energetic, and restless (American Psychiatric Association, 2013). An in-depth description of PG and its diagnostic criteria according to the DSM-V is provided in Chap. 4.

Another excessive behavioural pattern, that is Internet Gaming Disorder (IGD), has also been described in the "Conditions for further studies" section of the DMS-V, but the research literature is considered as less consistent on this and other behavioural disorders.

IGD is a pattern of "persistent and recurrent use of the Internet to engage in games, often with other players, leading to clinically significant impairment or distress" that results in a cluster of cognitive and behavioural symptoms, including progressive loss of control over gaming, tolerance, and withdrawal symptoms (for the complete lists of diagnostic criteria see DSM-V; American Psychiatric Association, 2013). The essential feature of IGD is the excessive and prolonged participation in computer gaming, typically group games, for many hours (usually even 10 h or more per day, at least 30 h per week), ignoring other normal activities. Individuals can resist without eating and sleeping for long periods while playing; personal, family, or vocational pursuits are neglected, interpersonal interactions and/or normal duties are avoided. The "boredom avoidance", rather than interaction or looking for information, is the main reason they reported for using the Personal Computer; besides, if prevented from gaming activity, they display emotional reactions, such as agitation and anger (American Psychiatric Association, 2013; Balconi & Finocchiaro, 2016; Balconi et al., 2017a, b).

The DSM-V working group found some behavioural parallels between IGD, PG, and SUD, encompassing neural responsiveness in specific brain areas (not limited to reward system structures), tolerance aspects, withdrawal, repeated ineffective attempts to avoid or stop playing, and impairment of normal functioning. So far, in the last version of DSM-V, other behavioural addictions such as exercise addiction, shopping addiction, or sex addiction were not included, because at that time there was scarce research literature and evidence to set the diagnostic criteria and descriptions needed to identify these behaviours as mental disorders (American Psychiatric Association, 2013).

More recently, the working group of the International Classification of Disease, 11th Edition (ICD-11) proposed to distinguish PG, compulsive sexual behaviour disorder, and excessive Internet Use from addiction and "Substance-Related Disorders" and included them in the recent version of the ICD-11 manual as Impulse Control Disorders (ICDs), defining ICDs as characterized "by the repeated failure to resist an impulse, drive, or urge to perform an act that is rewarding to the person (at least in the short-term), despite longer-term harm either to the individual or to others, marked distress about the behaviour pattern, or significant impairment in personal, family, social, educational, occupational, or other important areas of functioning" (World Health Organization, 2020).

It is worth noticing that despite the difference in the diagnostic classification system of these repetitive and addictive behaviours (perhaps due to the different goals of these manuals [Grant & Chamberlain, 2016]), the descriptions of the disorders are not in contradiction and share numerous points of contact.

1.2 Cognitive and Control Impairment in Addiction

Addiction refers to a process whereby a behaviour, which can function both to produce pleasure and provide an escape from internal discomfort, is employed in a pattern characterized by (a) recurrent failure to control the behaviour and (b) continuation of the behaviour, despite significant negative consequences (Goodman, 1990).

Two main cognitive functions have been emphasized as major components in the development and persistence of addictive states (i.e., Luijten et al., 2014), as underlined by the dual-process model (Field & Cox, 2008; Wiers et al., 2007). It can be stated that, on the one hand, the phenomenon of increased salience may be due to an impaired mechanism of reward, able to induce a sort of "reward bias" for potential rewarding cues, such as substance, but also video games or gambling stimuli (Park & Lee, 2011; Yen et al., 2012). Reward motivation significantly correlates with drug addiction (Balconi et al., 2014c; Knyazev, 2010), and the reward deficit syndrome was proposed as a possible contributing factor to the development of substance abuse disorders (Cao et al., 2007), since addiction may be related to greater receptiveness to the reinforcing effect of drugs and other similar rewarding stimuli (Logan et al., 1984; Vitaro et al., 1999). On the other hand, altered inhibitory skills have led authors to consider addiction as an impulse control disorder (Dell'Osso et al., 2008; Shapira et al., 2000). Response inhibition, as assessed through Go/No-go tasks, can be defined as the act of withholding or terminating a behavioural response, and is considered to be governed by a cognitive inhibitory process (Logan et al., 1984). A strong relationship between reduced impulse control and addictive behaviours, such as PG, substance, and alcohol abuse, has been evidenced (Barnes et al., 2005; Vitaro et al., 1999).

Inside the classification of ICDs, PG has been depicted as "a pattern of persistent or recurrent gambling behaviour, which may be online (i.e., over the internet) or offline, manifested by: (1) impaired control over gambling (i.e., onset, frequency, intensity, duration, termination, context); (2) increasing priority given to gambling to the extent that gambling takes precedence over other life interests and daily activities; and (3) continuation or escalation of gambling despite the occurrence of negative consequences" both at personal, family, social, educational, and occupational levels (World Health Organization, 2020). This definition of PG does not depart from its conceptualization as "behavioural addiction", since it shares the qualities of loss of control, tolerance, withdrawal, and the experience of negative consequences with substance dependence (American Psychiatric Association, 2013; Brewer & Potenza, 2008; Djamshidian et al., 2011; Marks, 1990; Verdejo-Garcia & Bechara, 2009; Weintraub et al., 2015). With this in mind, several studies focused on impulsivity trait, trying to define how it can impact gambling behaviour in turning into a compulsive and repetitive pathological habit over time.

Accordingly, it was shown a drug cue-reactivity is manifested by (a) a processing enhancement in the striatal brain regions related to motivation and reward and (b) typically fail to inhibit drug-oriented behaviour even when the consequences are

deleterious. Addictions "without substances", also called behavioural addictions [like PG or Internet addiction (IA)] show similar patterns (Luijten et al., 2014). At the neurocognitive level, it is suggested that the combination between these two components, that is, reward sensitivity and impulsiveness, may have an important role to play in explaining behavioural addiction. There is consistent evidence in this respect both at the structural and functional levels (see Kuss & Griffiths, 2012 for review). Current data indicate that, compared with controls, brain regions associated with reward, addiction, craving, and emotion (such as Nucleus Accumbens [NAcc], amygdala, insula, and orbitofrontal cortex [OFC]) are increasingly activated during game play and presentation of game cues, while furthermore, Internet addicts were found to have decreased grey matter volume in regions mediating cognitive control (such as supplementary motor area and dorsolateral prefrontal cortex [DLPFC]).

Brain imaging studies also stressed the importance of the prefrontal cortex (PFC) in addictive behaviours mainly through its involvement in a higher-order executive function as well as its regulatory function on limbic rewarding regions (Balconi & Finocchiaro, 2015; Baler & Volkow, 2006). More specifically, addictive states were defined by (a) hyperactivity in the emotional system, mediated by frontal and medial structures, such as OFC, anterior cingulate cortex, and amygdala, which exaggerated the rewarding impact of external reinforcing cues; (b) anomalous brain activity in DLPFC, which predicted the long-term consequences of a given action (Balconi & Finocchiaro, 2015); and (c) dysfunctions in the mesolimbic dopaminergic reward system, which can support conditioned attention allocation for dependence-associated stimuli rendering them especially salient (Adinoff, 2004), as already reported in substance abusers and impulsive individuals (Adinoff, 2004; Limbrick-Oldfield et al., 2013; Scheres et al., 2007). In this view, PFC was implicated in reward bias and whereas the left PFC was shown to be more implicated in approach-related and rewarding conditions, the right PFC was found to be more involved in withdrawal-related motivations and inhibitory mechanisms (Balconi & Mazza, 2009; Davidson, 2004; Harmon-Jones, 2004). Both approach and withdrawal motivations are paralleled by the reward and punishment contingencies, as shown in a recent electroencephalographic (EEG) study, which revealed a specific more left (reward-related) or right (punishment-related) higher brain responsiveness (Balconi et al., 2009a, 2012).

Finally, systemic blood pressure, pulse rate, and skin conductance were considered potential biological markers of arousal modulation related to the salience of a specific context or cue (Tupak et al., 2014). Among the others, skin conductance response (SCR) provides a useful measure of limbic function (Furmark et al., 1997; Lang et al., 2000). The significance of this measure for arousal modulation and attentional functions was previously demonstrated (Balconi et al., 2009b; Balconi & Pozzoli, 2008), as it may be considered a useful marker of the salience/relevance of some cues. Indeed, autonomic measures are generally related to the attentional and motivational significance of the eliciting context. The advantage of acquiring both the autonomic (arousal-related) and the central (EEG cortical-related) activities in studying addiction profiles stands in the possibility to better elucidate the reciprocal

interplay of the two compartments and to better describe the existence of anomalous response behaviour to the external stimuli. Indeed, recent research underlined the anomalous response by SCR in pathological decision-making (Bechara & Damasio, 2002; Dixon et al., 2010; Trotzke et al., 2015). However, whether and how behavioural addiction is related to rewarding mechanisms in response to Go/No-Go task, on the one hand, and how impulse control deficits are related to reward mechanisms, on the other, are actually unexplained (Kamarajan et al., 2008).

However, the exploration of the role of the executive functions in both behavioural and substance addiction appears limited, and it needs adjunctive clarifications.

The next paragraph will explore this aspect, pointing out the relevance of executive functions in developing and maintaining addiction.

1.3 Executive Functions: A Unique Object?

Although in the last century neuroscience and cognitive science achieved much progress, some "*grey areas*" still remain. One of these concerns the concept of "*Executive Function*" (EF) and the range of variations that arise from different intellectual traditions in clinical, developmental, and cognitive sciences, of which "*Executive Control*" (EC) (Logan, 1985; Neisser, 1967), and "*Cognitive Control*" (CC) (Botvinick & Cohen, 2014; Lenartowicz et al., 2010; MacDonald, 2008; Posner & Snyder, 1975) are the most utilized, besides being closely related, even though not coincident.

Among other related constructs, we remember the executive functioning (Diamond, 2013), effortful control (Eisenberg et al., 2004; Rothbart, 2011), reactive control (Derryberry & Rothbart, 1997), impulse control (Madden & Bickel, 2010), behavioural inhibition (Kagan et al., 1987), inhibition (Logan et al., 1984; Nigg, 2000; Simpson et al., 2012), executive attention (Kane & Engle, 2002; Nigg, 2017), controlled attention or interference control (Nigg, 2017), working memory (WM) (Baddeley, 2012; D'Esposito & Postle, 2015; Kane & Engle, 2002), top-down self-regulation (SR) (Barkley, 2012), emotion-, mood-, and affect-regulation (Gross, 2015), and more.

However, given the current framework, it cannot certainly be said that the large data production, as well as the models that have emerged throughout the last decades, have helped. Indeed, the major issue lies within the definition of the EF formulation itself due to so many models that have been proposed.

A first relevant question is that EF was considered as a unitary process, comparable to a single general process that can include and explain many phenomena and a variety of behaviours that broadly accepted as "*high-order cognitive processes*", such as inhibitory control, attention shifting, WM, goal-directed behaviour, and strategic planning (Goldstein et al., 2014). Within this tendency, some authors have considered EF similar to the general intelligence "*g-factor*" (a single factor underlying all, or almost all, the intellectual factors, that it is derived from the statistical factor analysis) (Duncan et al., 1995, 1996; Luria, 1973; Norman

& Shallice, 1986), while others considered EF isomorphic to a single process, such as WM (Kimberg & Farah, 1993). However, it seemed hardly conceivable that only one process could explain the several findings provided by the neuroscientific investigation (for reviews, see Jurado & Rosselli, 2007; Chan et al., 2008).

Therefore, in the current mainstream, EF is considered a network of subprocesses, relatively independent but interconnected, playing an important role in allowing humans to adapt to singular or novel situations. The EF concept is used to represent a wide class of cognitive abilities, by becoming a multifaceted mental concept that includes a vast amount of different components (Barkley, 2001, 2012).

More recently, Carter and Krus (2012) defined cognitive control as "*the ability to flexibly adjust behaviour in the context of dynamically changing goals and task demands*" (Carter & Krus, 2012), and Botvinick and Braver (2015) as "*the set of superordinate cognitive functions that encode and maintain a representation of the current task, marshalling to the task subordinate functions including working, semantic, and episodic memory, perceptual attention, and action selection and inhibition*" (Botvinick & Braver, 2015).

To summarize, EF deals with: (a) an intention to inhibit a response or to defer it to a more appropriate time in the future; (b) a strategic plan of action sequences; and (c) a mental representation of the task, including the relevant stimulus information encoded into memory and the desired future goal-state. Further work added other components to the list, which would play a role in action preparation, such as focusing and sustaining attention, generation and implementation of strategies, planning, and utilization of feedback (Glosser & Goodglass, 1990; Levin et al., 1991; Stuss et al., 1986).

We can also conceptualize EF as composed of four distinct components, including *volition, planning, purposive actions*, and *effective performance*. In these early theoretical proposals, a great emphasis was attributed to the action implementation process: hence, the "*executive*" label was the most fitting one.

1.4 Impairment of EF in Addiction

In general, the main difference between SUD and behavioural addiction is the presence of the chemical substance intake in the first case and its absence in the second one (where the substance is replaced by repetitive behaviour). Consequently, in PG and IGD, there are no physical signs of pharmacological withdrawal, although irritability, anxiety, and sadness can be described when the gambling/gaming activity is stopped or taken away.

The diagnosis of a SUD is based on a pathological pattern of behaviours related to the use of the substance, which can be grouped in four main areas (impaired control, social impairment, risky use, and pharmacological criteria), which can also be identified in behavioural addictions. Indeed, as we observed, several behavioural parallels were previously found between behavioural addiction (PG and IGD) and SUD, and those include neural responsiveness in specific brain areas (not limited to

reward system structures), loss of control over the behaviour, tolerance aspects, withdrawal, repeated ineffective attempts to avoid or stop playing, and impairment of normal functioning (American Psychiatric Association, 2013).

Regarding cognitive functioning, it is interesting noticing that these disorders share the progressive loss of control in terms of the amount of time dedicated to obtaining the substance or to be engaged in the repetitive behaviour. Progressively, all individual's activities revolve around the substance or the gambling/gaming behaviour. Moreover, they display impaired cognitive control in stopping their behaviour, both in terms of cutting down or regulating substance use, gambling, or gaming activities. Reduced levels of self-control, indicating a possible deficit in the inhibitory control brain networks, and impulsivity traits (mainly for SUD and PG) were found to characterize both substance and behavioural addictions. The psychopathology of EF in addiction will be deepened and better specified in Chap. 2. While more specifications mainly concerning EF impairment in PG will be provided in Chap. 4.

Instead, the main focus of this section will be oriented on two main processes related to EF impairment: the decisional process and the metacognition.

1.4.1 Decision-Making Processes

Authors suggested that some specific cognitive processes seem to be affected in SUD and behavioural addiction. Specifically, it seems that there are some structural effects of the substance on neural systems mediating cognition and motivation in decision-making. For example, Makris et al. (2008) found a correlation between the thinner prefrontal cortex and reduced performance during judgment and decision-making in addicts. It was suggested that brain structure abnormalities in addicts could be related not only to drug use but also to the predisposition of development addiction disease (Makris et al., 2008).

Thus, to identify and clarify the neural substrates that underlie decision-making may elucidate mechanisms contributing to continued high-risk behaviours in pathological gamblers (Balconi et al., 2014b, c). At least two underlying types of dysfunctions have been identified where reward signals turn in favour of immediate outcomes in the case of decisions: (1) hyperactivity in the emotional system, mediated by frontal and medial structures such as the OFC, Anterior Cingulate Cortex (ACC) and amygdala, which exaggerate the rewarding impact of external reinforcers, and (2) hypoactivity in the prefrontal cortex (such as left ventromedial areas, VMPFC, and mainly the DLPFC), which predicts the long-term consequences of a given action and that is a critical component for working memory and executive processes. Damage or dysfunctional conditions to either of these systems can alter the normal functioning of the decisional processes (Balconi et al., 2014b).

Furthermore, anomalous brain activity was found in behavioural addiction like PG, and it seems that the same brain pathways are affected both in substance and non-substance addiction disorders. Potenza and Colleagues (2003a) investigated

impulse control behaviour using functional magnetic resonance imaging (fMRI): PG group performed a Stroop task to test attention and response inhibition during the presentation of congruent and incongruent stimuli, and the authors found that in response to infrequent incongruent stimuli, the PG group showed a decreasing activity in the left VMPFC compared to control group. Positron emission tomography (PET) studies indicate that substance-dependent individuals show altered prefrontal activity on the Iowa Gambling Task (IGT).

Specifically, reductions in right prefrontal activity during decision-making may reflect impaired working memory, stimulus reward valuation, or cue reactivity in substance-dependent individuals (Tanabe et al., 2007). In our study, we demonstrated that SUD group showed a strong lateralization effect in DLPFC, which is involved during the decisional process: the SUD group revealed an increase of left hemisphere activation in response to immediate reward choices, and this cortical unbalance effect seems to be related to the lower performance in IGT (Finocchiaro & Balconi, 2015).

In our recent studies, we investigated the motivational traits, considering the approach or withdrawal tendencies, in drug dependence and subclinical individuals. Considering the Behavioural Inhibition System (BIS) and Behavioural Activation System (BAS) scale (Carver & White, 1994), we focused on the BAS reward trait that seems to characterize addicted personality (Balconi et al., 2014b, c, 2014c; Balconi & Finocchiaro, 2015). We considered the hypothesis that individuals with the high-activation system in the motivational dimension (high-BAS) could show similarity with the addicted profile (Finocchiaro & Balconi, 2015). We postulated that high-BAS individuals have a similar dysfunctional mechanism in the decision-making process (lower performance in IGT) related to a higher left hemisphere activation and could be more vulnerable to develop addiction even when they were not a clinical population. We considered this "cortical unbalance effect" as a critical marker of dysfunctional decision-making in high-risk populations, and a factor able to explain the tendency to opt in favour of more reward-related conditions (Finocchiaro & Balconi, 2015).

Literature shows that deficit in cognitive performance is correlated with altered brain activity also in IGD (Ko et al., 2014). A recent fMRI study focused on response inhibition using a Go/No-go paradigm in a population of IGD, which showed higher brain activation in IGD while they were processing response inhibition over the left orbital frontal lobe and bilateral caudate nucleus in comparison to the control group; moreover, the activation over the right insula was lower in the individuals with IGD (Ko et al., 2014). Thus, the authors suggested that fronto-striatal network involved in response inhibition, which contributes to error processing, could be damaged in individuals with IGD: for this reason, they could have impaired insular function in error processing, and lower abilities to maintain their response inhibition performance.

1.4.2 Metacognitive Processes

Another factor that may be correlated with drug abuse and behavioural addiction is the absence of explicit cognitive knowledge of the possible effect and/or consequences of one's own behaviour; this self-monitoring ability has generally been referred to as "metacognition", "cognition about cognition", or "metacognitive abilities" (i.e., Toneatto, 1999).

In healthy people, it is well-known that metacognitive abilities—the high-order function of self-monitoring, updating, and adjusting maladaptive behaviours and "to have an insight about the quality of one's decision" (Brevers et al., 2013)—have an important role in the regulation of decision making.

Still, metacognition is theoretically strongly connected to decision-making, and it has been defined as the self-monitoring skill to reflect on one's self-performance and to discern between correct and wrong choices and results. It mainly engages prefrontal brain areas, in which are located EFs and higher-order processing of cognitive processes engaged in learning and self-awareness.

So far, metacognitive skills and their connection to PG behaviour have been more deeply investigated in the field of addiction studies. Exploring metacognition in gambling, Brevers et al. (2013) described it as "the condition where gamblers behaviour becomes firstly led by a potential immediate payoff, at the expense of substantial losses in the long-term reflect the lack of conscious monitoring of the consequences of one's actions". Thanks to the use of a post-decision wagering procedure after the IGT, Brevers et al. (2013) highlighted an impairment in metacognition in gamblers' population.

Mechanisms of metacognition have been shown to mainly recruit the prefrontal structures (i.e., Schmitz et al., 2004), and they were associated with "supervisory" functions such as task contingencies, attentional set-shifting, and the ability to self-monitor the behavioural effects of one's actions (Dalley et al., 2004). Here again, the inability to self-monitor one's own actions has been clearly linked with addiction (i.e., Park et al., 2010).

For further expanding this concept, we recently investigated electrophysiological and hemodynamic cortical correlates, but also metacognitive abilities, in Parkinson's Disease (PD) patients with PG (Angioletti et al., 2019, 2020; Angioletti & Balconi, 2019; Balconi et al., 2018a, b). In fact, some patients taking dopaminergic medications, such as PD patients, may experience urges to gamble as a side effect. Not all PD patients, however, develop medication-associated PG and the fact that most patients have developed PG under dopamine replacement therapy indicates an underlying mechanism of susceptibility to PG in patients with PD and that dopamine agonists most likely cause this mechanism (Heiden et al., 2017; Voon, 2017).

Nevertheless, the metacognition has been little studied in this subgroup of patients with PD and PG, and previous research yielded mixed results. Indeed, a deficit in metacognition has been reported in previous studies (Palermo et al., 2017; Pineau et al., 2016). In contrast, a prior work found a preserved and greater cognitive metacognition into thoughts and behaviours in PD with ICDs, meaning they are

aware of their executive dysfunctions and difficulty in resisting in engaging impulsive behaviours, if compared to PD patients without ICDs (Mack et al., 2013).

Within our recent line of research, which has focused on this theme, findings highlighted that patients with Parkinson Disease (PD) and Parkinson Disease Gamblers (PDG) showed higher levels of impulsivity than PD controls as reflected by clinical scales and behavioural measures. Also, PDG displayed a worse performance at IGT although they are stated to have used an efficacious strategy, suggesting then an erroneous metacognitive representation. Overall, these results suggested that high levels of impulsivity combined with an explicit metacognitive bias on self-efficacy could intervene in the persistence of PG in PD patients (Angioletti et al., 2020). Interestingly, these studies claimed the need for a shared tool to deepen metacognition in PD patients specifically with PG.

1.5 Commonalities and Differences for EF and Neural Circuits in Substance and Behavioural Addictions

1.5.1 Brain Dysfunctions

Neuroscience studies have identified addiction as a chronic brain disease with genetic, neurobiological, and environmental components which lead to changes in whole brain functioning and long-lasting impairments to specific brain structures involved in attention, WM, decision-making processes, judgment, and gratification, with a negative consequence on cognition performances, emotion regulation, and social adaptation (Baler & Volkow, 2006; Bechara & Damasio, 2002; Bechara & Martin, 2004; Li & Sinha, 2008; Li et al., 2013; Yan et al., 2014).

The principal neural circuits that seem to be involved in the "addicted brain" are the mesostriatocortical system and the frontocortical area (Volkow et al., 2013). Indeed, repeated drug administration triggers neuroplastic modifications with a modified Dopamine (DA) activity in the mesocorticolimbic circuit, an alteration of glutamate neurotransmission, and a cortical excitability modulation, which influence cognition, emotion, and behaviour (Volkow & Baler, 2014). Decreasing of DA's stimulation in the NAcc, which is a major component of the Ventral Striatum (VS) and a key structure involved in mediating motivational and emotional processes, creates a strong consolidation on the motivational system in order to take more substance. It enhances the brain's reactivity to drug cues, reduces the sensitivity to non-drug rewards, as consequences of weakening self-regulation and increasing the sensitivity to stressful stimuli and dysphoria (Volkow & Li, 2004; Volkow & Morales, 2015). Moreover, neuroimaging studies using fMRI or PET suggest a reduction in DA (D2) receptors and a decrease in the release of DA in the VS (Volkow et al., 2003) which contribute to reducing the sensitivity to natural reinforcements in addicts' population. Another study showed a hyperactivity of the OFC connected to the limbic system (Yamamoto et al., 2014). Specifically, the

literature suggests that OFC is involved in decoding, representing, learning, and reversing associations of stimuli to the reinforcers and, also, in controlling reward-related adjustment and punishment-related behaviour (Rolls, 2004): thus, increasing of OFC activity in addicts' population is probably linked to the extreme focus on drugs-related rewards.

1.5.2 Brain Circuits: The Role of Brain Connectivity

Whereas it is widely accepted that addictive drug use is related to the abnormal functional network in an addict's brain, in the last years, several neuroscientific studies aimed to identify this type of abnormality within the *brain networks* implicated in addiction, often by measuring resting-state functional connectivity, which offers a direct measure of functional interactions between the brain areas (Kelly et al., 2011). Ma et al. (2010) found that chronic heroin users showed increased functional connectivity between NAcc and ventral/rostral ACC, between NAcc and OFC, and between the amygdala and OFC, but reduced functional connectivity between PFC, OFC, and ACC. Authors argued that findings may provide additional evidence supporting the theory of addiction that emphasizes enhanced salience value of the substance and ineffective cognitive control of the cues-related condition, which could have a severe role in the maintenance of the addictive behaviour (Ma et al., 2010).

Individuals with substance addiction showed greater connectivity of the right insula cortex with the dorso-medial prefrontal cortex, inferior frontal gyrus, and bilateral DLPFC (Cisler et al., 2013). These data confirm the hypothesis that addiction is related to altered functional interactions of the insular cortex with prefrontal networks: thus, this could have a negative influence on cognitive control and decision-making processes.

Moreover, the literature confirms the hypothesis that IGD shares similar neurobiological abnormalities with SUD. In a recent resting-state fMRI study, it was found that the IGD group showed increased functional connectivity in the bilateral cerebellum posterior lobe and middle temporal gyrus, in spite of decreased connectivity in the bilateral inferior parietal lobule and right inferior temporal gyrus, and that these different patterns of brain activity in IGD group were correlated with the severity of IA and impulsivity (Ding et al., 2013). Often addiction models emphasize the role of disrupted frontal circuitry supporting cognitive control processes.

However, it is useful to consider addiction-related alterations in functional interactions among brain regions, especially between the cerebral hemispheres, which are only occasionally analysed. Kelly et al. (2011) observed reduced prefrontal inter-hemispheric connectivity in addiction. Specifically, they demonstrated a severe cocaine-dependence-related reduction in inter-hemispheric connectivity among nodes of the dorsal attention network (frontal and parietal areas) which were associated with self-reported attentional deficits. Their findings

confirmed a link between chronic abuse of cocaine and disruptions in brain circuitry supporting cognitive control (Kelly et al. 2011).

Another study focused on IA investigated inter-hemispheric functional and structural connectivity in adolescents (Bi et al., 2015). Authors showed decreased activity of DLPFC which was negatively correlated with the duration of IA, and also lower integrity of white matter and lower connectivity in the Corpus Callosum. Moreover, in a Go/No-Go study, adolescents with IA fail to recruit the indirect frontal-basal ganglia pathway, which was engaged by response inhibition in healthy subjects (Li et al., 2014). All this evidence indicates that addictive disorders (with or without substance) have similarities in the neural basis of poor impulse control, and this fact is important for understanding the neurobiological mechanisms of addiction.

1.6 Reward Mechanisms (RM) in Substance and Behavioural Addiction

1.6.1 RM in Substance Addiction

As we have seen, the psychoactive substances (such as amphetamines, cocaine, alcohol, nicotine, marijuana, heroin) act directly or indirectly on a structure of the midbrain causing the large release of DA (Goodman, 2008; Volkow et al., 2013; Volkow & Baler, 2014). DA is produced by neurons in the Ventral Tegmental Area (VTA) of the midbrain, and it is released in the synapses of NAcc (Bloom & Koob, 1988). The NAcc is involved in pleasure and reward sensation; indeed, many drugs that cause addiction are active in this area or in the VTA, which has neural connections to the NAcc.

Furthermore, the VTA is connected to the amygdala which has an important function in emotional and social processing (Adolphs et al., 1995), thus increased stimulation in the VTA leads to a sense of intense pleasure and gratification. Decreased DA's stimulation in NAcc, due to repeated use of drugs, creates a strong consolidation on the motivational system in order to take more substance, which does not occur for natural rewards (Volkow & Li, 2004). These limbic structures (VTA, amygdala, and NAcc) are connected with the VMPFC whose function is the regulation and the processing of positive and negative emotional states, reward sensation, motivation, and socially acceptable behaviour. Finally, the DLPFC is important in working memory, regulation of attention, and behaviour based on emotional states. The organism tries to maintain the baseline level of DA in VS, by natural reinforces. Yet, neuroimaging studies (fMRI/PET) suggest that reduction observed of DA (D2) receptors and reduction in the release of DA in the VS (Volkow et al., 2002) contributes to reducing the sensitivity of addicts to natural reinforces. Also, an hyperactivity of the OFC was found below the limbic system (Volkow et al., 2003), probably due to the extreme focus by addicts on substance-related rewards.

An fMRI study has shown a reduction of activity in the mesolimbic reward system in pathological gambling (Reuter et al., 2005): this supports the hypothesis that reduction of the activation of VS induces the organism to seek stronger reinforces even in non-drugs addiction, to compensate the dysfunctional activation of VS. Moreover, it is possible that the negative emotional state associated with acute abstinence from substances or gambling (such as consequences of the reduction of the reward neurotransmitter function) contributes to maintain the addiction despite the adverse consequences emerging from the pathological behaviour.

Thus, there is strong evidence that the dopaminergic system is the major substrate of reinforcement for both natural rewards and addictive drugs (Ikemoto & Bonci, 2014). Specifically, rewards are positive reinforcements that increase the frequency of approach behaviour, necessary for survival and well-being, control of homeostatic function, and goal-directed behaviour; instead of punishments that are negative reinforcements that increase the frequency of withdrawal behaviour (Gray, 1981). In general, rewards imply hedonic consequences (pleasure); learning cues; assigning value and motivational status (salience).

Dysfunctions of reward systems can induce patients to persist with the maladaptive behaviour, i.e., the activation of DA systems appears to be accompanied by positive emotional arousal characterized as "high" (euphoria), instead of a hedonic sensory pleasure. Furthermore, as an addiction develops, the pleasure induced by drugs decreases, the craving increases, and the maladaptive consequences persist. The learning cues predict rewards and actions to drug consumption. Finally, salience attribution induces patients to select among numerous behavioural options the one that permits them to obtain a specific substance (or goal-rewarding) and to ignore natural reinforces.

1.6.2 RM in Behavioural Addiction

The current state of knowledge from neuroscience studies suggest that there may exist a common pathological pathway between SUD and non-substance related disorder (i.e., gambling, food, sex, or Internet addiction), involving dysfunctional reward mechanisms and deficit in cognitive decisional processes. The neurobiological patterns of the addictive behaviours are similar: i.e., there is a reduction in DA (D2) receptors on compulsive feeding (Wang et al., 2002) and gambling-related to deficits of the frontal cortex in pathological gambling (Potenza, 2008). Also, it has been shown that stressors affect relapse in these disorders (Ledgerwood & Petry, 2006).

More specifically, several studies showed that behavioural addiction as PG or IA shares the same dysfunction in reward mechanisms and cognitive control with SUD (Wareham & Potenza, 2010; Yuan et al., 2011). Specifically, a reduction of the activity was found in the mesolimbic reward system in PG (Reuter et al., 2005), and structural abnormalities in grey and white matter volume in left posterior limbic and DLPFC which are linked to functional impairments in cognitive control in IA (Yuan

et al., 2011). Thus, altered prefrontal activity with enhanced striatal responses to addicted drug or addicted behaviour-related salient stimuli perpetuates habitual drug or behavioural object seeking despite negative consequences. As for drug cue-related brain stimulation in SUD, the same brain area activation (OFC, DLPFC, anterior cingulate, NAcc) was observed for game cues in individuals with IGD (Dong et al., 2011; Ko et al., 2009).

In our recent study, we tested reward sensitivity in Cocaine Addiction (CA) population (Balconi & Finocchiaro, 2015). We focused on the behavioural motivational responses that are crucial to the generation of emotions relevant to approach (reward) and withdrawal (inhibition) in the decisional process (Gray, 1981). Carver and White (1994), according to Gray's model, developed the BIS/BAS scales, a self-report measure composed of 24 items; also, BAS includes three subscales (Reward, five items; Drive, four items; and Fun Seeking, four items). The BAS seems to activate behaviour in response to conditioned, rewarding, and non-punishment stimuli, and it is supposed to be mediated by dopaminergic pathways from the VTA to the NAcc and VS (Fowels, 1994).

The normal level of BAS functionally affects positive emotional attitude, but extreme levels of BAS have been linked to impulsivity disorders such as Attention-Deficit (ADHD) and hyperactivity disorder, or addictive diseases, risk, and antisocial behaviour.

Instead, the BIS appears to be preferentially activated by stimuli conditioned as being aversive, thus the BIS is responsive to non-reward stimuli, preventing individuals from negative or painful outcomes. A dysfunction in the direction of hyperactivity of this system could generate pathological disorders such as Generalized Anxiety Disorder (GAD) or Obsessive-Compulsive Disorder (OCD). Several studies showed a strong correlation between BIS/BAS systems and the cortical brain activity. Specifically, a greater left frontal activity seems to characterize individuals with higher BAS and lower BIS scores (Harmon-Jones & Allen, 1997; Sutton & Davidson, 1997). On the other hand, an increase in right frontal activity seems to be related to higher BIS and lower BAS sensitivity (Balconi & Mazza, 2009, 2010).

Interestingly, in a recent study aimed to determine the relation between BIS and BAS and the increased risk for IA, only BIS and BAS-fun seeking subscale predicted IA (Park et al., 2013). The importance of BIS has been repeatedly confirmed in previous studies on BIS/BAS and IA (Meerkerk et al., 2010; Yen et al., 2012).

In different works, we related the BIS/BAS scale to the IGT, which is a typical risky decision-making test developed by Bechara et al. (1994) to experimentally capture the decision-making deficits of patients with VMPFC damage. The IGT is a sensitive tool able to discriminate people with frontal lobe dysfunctions, in addition to adults with VMPFC damage (Balconi et al., 2014b, c; Balconi & Finocchiaro, 2015; Bechara & Martin, 2004). Other groups perform poorly on the task, including people who report being high in risk-taking behaviours and people who abuse substances, such as drugs and alcohol (Bechara et al., 1994; Brevers et al., 2013).

The IGT requires continuous selections to be made from decks of cards with varying rewards and punishments. Some decks have high initial rewards but result in high punishments over time and thus are disadvantageous in the long run. Other

decks have lower initial rewards but also lower punishments over time, making them advantageous in the long run. We supposed that the BAS was a predictive marker of dysfunctional behaviour in IGT, and, also, we focused on self-reported metacognitive measures concerning the decisional process (Balconi et al., 2014b). We found that an increase in the reward sensitivity (higher BAS and BAS reward) explained a poorer performance on the IGT and dysfunctional metacognition ability (unrealistic representation) in the cocaine addicts (CA) group compared with the control group. Generally, a high level in the BAS reward responsiveness may be considered a predictive measure of risk-taking and dysfunctional behaviour, not only in pathological (CA) individuals but also in subclinical individuals (Balconi et al., 2014c).

Diminished activity of the VMPFC has been associated with impulsive decision making in risk-reward assessments in pathological gamblers (Potenza et al., 2003a) and with a tendency to discount rewards rapidly and perform poorly on decision-making tests in IA individuals and pathological video gamers (Brand et al., 2014; Irvine et al., 2013).

However, some evidence suggests preserved decision making and sensitivity to punishment in individuals with Problematic Internet Use (PIU) (Ko et al., 2010; Nikolaidou et al., 2016). A recent study compared the IGT performance of individuals with PG, with a clinical PIU sample (namely, IGD) and controls: despite both patient groups performing worse in the IGT than healthy controls, IGD patients performed poorly only at the beginning of the task. This evidence suggests that though both groups of patients tend to process information more spontaneously when facing a rewarding condition, but the monetary dysfunctional effect mainly occurs for PG patients, in contrast, IGD tended to shift toward more adaptive decision-making strategies (Wölfling et al., 2020). Although the evidence related to decision-making processing in individuals with PIU showed a halfway profile between the preserved function and a pathological condition, this mechanism is still understudied, and research on larger clinical PIU samples is needed.

Individuals with CA often evidence poor cognitive control: in a recent study, Worhunsky et al. (2013) used the fMRI method to investigate fronto-cingular connectivity network, which was supposed to underlie cognitive control processes, in CA patients, who were asked to perform a Stroop task for testing selective attention and inhibition of control. A reduced connection of a "top-down" fronto-cingular network contributing to conflict monitoring correlated with better treatment retention was found. However, greater involvement of two "bottom-up" subcortical and ventral prefrontal networks related to cue-elicited motivational processing correlated with abstinence during treatment. Authors argued that these brain networks (fronto-cingular, subcortical, and ventral prefrontal) linked to cocaine abstinence and treatment retention could represent important targets in novel treatment for CA. Moreover, another study demonstrated that cocaine users had difficulties inhibiting their behaviours, particularly when working memory demands during the cue-induced craving for the drug, and they showed reduced activity in the anterior cingulate and right prefrontal cortex, which is thought to be critical for cognitive control (Hester & Garavan, 2004).

Poor inhibitory control has also been widely described in PG (for a review see Chowdhury et al., 2017), along with decreased activity in the frontal cortex and OFC, caudate/basal ganglia, and thalamus, while viewing gambling scenarios (Potenza et al., 2003b).

Also, neuroimaging studies suggested a decreased grey matter volume in the left ACC and in individuals with IGD that might contribute to the disruption of EF (Han et al., 2012; Lin et al., 2012), also, compared with healthy controls, individuals with IGD are more likely to exhibit impaired response inhibition (for a review see Argyriou et al., 2017).

1.6.3 The Cortical Unbalance Model: Neurophysiological and "Attitude" Effect

As we previously underlined, neuroscience studies showed that addiction is related to alterations to the brain's motivation and reward system. Specifically, the transition from casual drug use to addiction disease seems to be associated with the reward-bias circuit, neurocognitive impairments, salience attribution to rewarding-stimuli (Balconi et al., 2014b; Bechara, 2005; Goldstein & Volkow, 2002), neuroadaptation in memory circuits (Volkow et al., 2003), and compromised in metacognition and self-awareness (Balconi et al., 2014b; Goldstein et al., 2009). Evidence shows that drug dependence may be related to higher receptiveness to the reinforcing effects of drugs, reward-related (Balconi et al., 2014c).

Indeed, it has been suggested that addiction is characterized by a dysfunctional preference for immediate rewards instead of delayed rewards, which manifest as impulsivity. This hypothesis is supported by fMRI studies which showed an increase in amygdala activity in response to drug-related cues (Volkow et al., 2013). Some of the individuals with addictions that match VMPFC patients are characterized by insensitivity to future consequences (Bechara, 2005); they are unaware of future positive or negative consequences, and instead, they are driven by immediate rewards (Balconi et al., 2014c). Although one subgroup of addicts does not show deficits in the decision making, persisting in drug abuse could lead individuals with SUD to ignore the long-term negative consequences of their actions for immediate gratification or relief from uncomfortable states.

It was argued that many drug abusers seem to have an alteration of the mechanisms that prompt approach-behavioural processes, which are accompanied by positively affective states (Solomon & Corbit, 1974; Ikemoto & Bonci, 2014; Balconi et al., 2014b, c, 2014c).

According to Gray's BIS/BAS model (Gray, 1981), previous research works indicated that behavioural motivational responses related to personality characteristics are essential for two main aspects: for generating emotions, and approach (reward) and withdrawal (inhibition) behaviours in the decisional process (Balconi et al., 2014b, c).

With respect to reward mechanisms, the BIS/BAS scale is a valuable instrument for evaluating possible anomalous reward sensitivity in neuropsychiatric populations, such as addictions, relative to healthy subjects (Balconi et al., 2014b, c; Carver & White, 1994). It permits to quantify the prevalence of BIS or BAS in individuals. As we have seen, the BAS motivational component has been conceived as a mechanism sensitive to compensation, incentive stimuli, reward, and non-punishment, involving actions directed towards a gain and away from a loss (Carver & White, 1994).

Therefore, approach behaviour is promoted by reward, which induces a positive reinforcement for action, whereas avoidance behaviour (withdrawal) is reinforced by punishment. A normal level of BAS has a functional influence on positive emotional attitudes, while severe BAS and reward sensitivity levels have been related with impulsivity disorders (Newman et al., 2005), and high levels of BIS have been associated with anxiety disorders (Balconi et al., 2014c; Balconi & Mazza, 2009; Quay, 1988). Previous studies found a relationship between impulsivity and the BAS construct in SUD (Dawe & Loxton, 2004). Also, a direct association has been found between the BAS subscales and substance abuse (Balconi et al., 2014c).

Moreover, evidence suggests that left and right frontal brain activity may reflect the strength of BAS and BIS activity. Empirical data showed that resting frontal EEG asymmetry is related to measures of BAS sensitivity; specifically, it was found that subjects with major left frontal activity showed higher levels of BAS sensitivity (approach motivation), whereas subjects with higher BIS scores showed greater right frontal activation (Sutton & Davidson, 1997). Recent studies confirmed a correlation between the hemispheric activation asymmetry to BIS/BAS system: the left PFC is implicated in approach-related motivations and emotions, whereas the right PFC was found to be involved in withdrawal-related motivations and emotions (Balconi & Mazza, 2009; Davidson, 2004).

A crucial point is that BIS/BAS system has a cortical correlation with the PFC structures: while the left PFC activity was shown to be involved in approach-related motivations (appetitive) and positive emotions (reward processing), it was found that the right PFC activity was involved in withdrawal-related motivations (aversive) and negative emotions (punishment) (Balconi & Mazza, 2009; Davidson, 2004). Former studies showed that individuals with SUD, PG, or high-level of BAS reward sensitivity exhibited substantially more risky decision-making, preferring a greater possible reward even at a higher penalty risk. In addition, in these populations, their electroencephalographic behaviour showed a left PFC (DLPFC and ACC) frontal hemispheric activation asymmetry at the electrophysiological level, suggesting enhanced sensitivity to more risky choices (Balconi et al., 2014b, c).

According to previous data in our recent research, we hypothesized that the *hemispheric imbalance* between the left and right frontal cortex would characterize the decisions of subjects who show a higher reward trait and riskier behaviour, with a possible higher left hemisphere activity. Thus, we explored the relationship between the motivational system, using the BIS/BAS scale, and the hemispheric lateralized activity, with EEG measure (neurophysiological recording of spontaneously electrical brain activity by electrodes placed on the scalp), during a decisional

risky task (IGT) in CA. We found an increased response to immediate rewarding events, related to an increasing in left hemisphere cortical activity in CA, and lower performance at IGT comparing healthy subjects: such as there is a sort of reward bias which induced the addicts to overestimate the immediate reward and to ignore the delayed reward (Balconi et al., 2014c). Hence, the question is whether there are some individuals who may be psychophysiologically vulnerable, or at high risk, to develop an addiction, compared to other people who demonstrate normal decision-making abilities to behavioral tasks or neurophysiological tests.

This result may suggest that there are bio-psychological markers that can act in general to predispose individuals to addiction behaviours. Modulation of brain oscillations may be considered a valid measure of brain activation: indeed, the measurement of EEG Event-Related Potential (ERP) and frequency band provides a potentially direct assessment of cortical processing involved in behaviour. In the frontal system, resting EEG studies have shown frontal hemispheric activation asymmetry in favour of the right PFC that reflects an individual predisposition to respond in terms of withdrawal-related behaviour (Balconi & Bortolotti, 2012; Davidson, 2004): therefore, hypoactivity in the right PFC might be considered as a dispositional marker of higher risk-taking behaviour. Indeed, in a recent study focused on risky decisions, subjects opted for significantly riskier choices after inhibition of the right lateral PFC by Transcranial Magnetic Stimulation (TMS). They chose a larger potential reward even at a larger risk for punishment (Knoch et al., 2006).

More generally, EEG studies showed a different activity in neural connectivity in drug abusers during both acute and chronic abuse. Specifically, in a recent review, Parvaz et al. (2011) focused on the major studies which reported significant changes in neural connectivity in drug abusers, such as increasing to high band frequencies (alpha, beta) linked to the elevated feelings of drug effects such as euphoria in marijuana self-administration; and increasing in beta, delta, and frontal alpha activities in CA. Besides, in response to drug cues, data suggest an increase in cortical activation in alcohol-dependent patients and CA for high beta and low alpha spectral power. In ERP studies, higher cortical activation in response to drug cues was shown, i.e., increased amplitude of P300 in alcohol and nicotine-addicted patients (Parvaz et al., 2011).

1.7 EEG Approach to Addiction: BIS/BAS and Cortical Oscillations

As impairment in inhibitory control is classically considered as the cornerstone of addictive states, most EEG studies in IA focused on the reflective system, while concerning the automatic-affective system, it has to be underlined that current data remain very preliminary due to the small number of available studies (see D'Hondt & Maurage, 2017).

However, with specific reference to IA, limited studies explored the relationship between addiction, impulsivity, and brain activity by focusing on EEG (Kamarajan et al., 2004). Ample range of brain oscillations was previously used to test brain correlates of different types of addiction (Balconi et al., 2015; Balconi & Finocchiaro, 2015; Finocchiaro & Balconi, 2015). Specifically, delta band responses were assumed to mediate signal detection and decision making (Schürmann et al., 2001), whereas theta functions were mainly attributed to different cognitive processes, such as inhibitory mechanisms (Klimesch et al., 2001). It was also found that in some specific addiction behaviour (i.e., alcohol dependence), patients showed a significant reduction in delta and theta power during No-Go trials as compared with controls. This reduction was prominent at the frontal region and suggests a deficient inhibitory control and information-processing mechanism. Furthermore, both higher frequency bands (i.e., beta and gamma) are associated with response inhibition. Two EEG studies assessed the reflective system in IA about online computer gaming by investigating resting-state activities, which reflect non-task-related cognitive mechanisms (Barry et al., 2010; Choi et al., 2013). A first study showed a decreased absolute power in the beta band (Choi et al., 2013) in IA, previously related to task-related impulsivity observed in ADHD patients (Snyder & Hall, 2006). IA also presented increased absolute gamma band power. Moreover, changes in gamma band have also been associated with impulsivity (Barry et al., 2010).

Studies with frequency band analysis focused on modification in cortical oscillations during cognitive tasks in different types of addiction behaviours. Specifically, several studies used the EEG method to analyse the asymmetry between PFC activity in the left and right hemispheres and the associations to affective and motivational behaviour, and clinical outcomes (Coan & Allen, 2003; Davidson, 2004; Sutton & Davidson, 1997). Coan and Allen (2003) found that the PFC asymmetry index may be considered as an indicator of risk for an individual's propensity, and it could be useful in prognoses and treatment interventions.

As we have seen, resting EEG studies have shown that frontal hemispheric activation asymmetry in favour of the right PFC reflects an individual predisposition to respond in terms of withdrawal-related behaviour (Davidson, 2004; Harmon-Jones, 2004). Alpha power modulation may be considered a valid measure of brain activation, and it was largely applied to find distinct responsiveness by the two hemispheres to different cognitive or emotional tasks (Newman et al., 2005). About the frontal system, reduction in alpha power (that is more cortical activation) in the left frontal brain was found after reward trials, whereas punishment conditions induced reduction in alpha power in the right frontal brain (Buss et al., 2003; Sobotka et al., 1992). To test this lateralized effect based on IA and BAS construct, a specific attentional inhibitory task was adopted, that is the Go/No-go task, that can be defined as the act of withholding or terminating a behavioural response and it is considered to be governed by a cognitive inhibitory process (Logan et al., 1984).

Internet Addiction Test (IAT) (Young, 1998) as a vulnerability marker of potential IA were applied to characterize a sample of young subjects presenting high- or low-IA profile, during the performance of a Go/No-go task in response to specific potentially rewarding cues (videos representing online gambling and videogames or

neutral contexts as sports game). Indeed, IAT measures the subjective profile in terms of absence or presence of IA, furnishing specific cut-off (from absent to severe IA). Whereas the low-IAT shows no IA, high-IAT may reveal addiction vulnerability from moderate to severe (Young, 1998). Thus, alpha frequency band (8–10 Hz) and brain activation in specific cortical sites and personality traits (BIS/BAS) were considered as predictive components to explain a potential web addiction profile.

Regarding the association between cortical activity and advantageous/disadvantageous choices in IGT, in our research we focused on the hypothesis that left hemisphere dominance should index greater approach-attitude tendency, maybe reinforced by and related to the positive experience of immediate reward, which is higher in the disadvantageous decks. Furthermore, left dominant individuals should indicate less sensitivity to punishment than right dominant individuals. Thus, in our recent work, we aimed to investigate the decisional making process and the effect of the reward-sensitivity, considering the BAS-Reward construct, on the IGT performance. We considered the impact of the BAS motivational system on the frontal left and right cortical activity on individuals' decisions. More specifically, we hypothesized a specific lateralization effect, which is supposed to be related to the increased activation of the left (BAS-Reward-related) hemisphere, in the delta, theta, alpha, and beta cortical bands for high-BAS individuals.

Also, behavioural responses (gain/loss options), metacognition dimensions (self-knowledge, strategic planning, flexibility, and efficacy) were investigated. Thirty participants were divided into high-BAS and low-BAS groups. In comparison with low-BAS, the high-BAS group showed an increased tendency to opt in favour of the immediate reward (losing strategy) instead of the long-term option (winning strategy). Moreover, the high-BAS group was more impaired in metacognitive monitoring of their strategies and showed an increased left hemisphere activation when they responded to losing choices. A "reward bias" effect was confirmed to act for high BAS, based on a left hemisphere hyperactivation (Balconi et al., 2014c). In another work, we considered the addict population and we tested specifically the activity of alpha band modulation during an IGT performance. Activity in the alpha band oscillations is used as an inverse index of cortical activity, which assumes that a brain region producing alpha rhythms is in a state of cortical loafing. Thus, the more alpha appearing in the EEG track of a brain region, the less active or engaged it is.

We found that the SUD group increased the tendency to opt in favour of the immediate reward, which is a losing strategy more than the long-term option, which is a winning strategy, compared to the control group. Moreover, higher reward-subscale scores were observed in SUD. Finally, SUD showed an increase in left-hemisphere activation in response to immediate rewarding choices. We conducted regression analysis for BAS sub-scales, and we found that higher BAS traits could explain this unbalanced left-hemispheric effect related to the main behavioural deficits (Balconi et al., 2014b). Moreover, we found the same cortical lateralization effects in a sample of high-risk individuals with high scores on the BAS scale, only for alpha band analysis. Thus a "reward bias" effect was supposed to explain both the bad strategy and the unbalanced hemispheric activation for high-BAS and more

risk-taking subjects. These findings could have relevance for prevention in high-risk populations (Balconi et al., 2014c, 2015; Finocchiaro & Balconi, 2015).

1.8 Impulsivity Control and Psychological Traits

Personality traits of impulsivity and sensation-seeking are highly prevalent in SUD individuals (De Wit, 2009). In particular, sensation-seeking has been linked with the onset of substance abuse, and impulsivity has been associated with the development and maintenance of dependence (Belin et al., 2008). Impulsivity seems to be a pathological trait marker of addiction, i.e., impulsive choice in SUD individuals correlates with impaired function of prefrontal cortical areas, such as the OFC. In a study with Heroin Dependent (HD) patients, higher impulsivity scores measured by the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995) were related to significantly enhanced intrinsic Amygdala Functional Connectivity (iAFC) (Xie et al., 2011). Thus, altered iAFC network connectivity in HD patients may contribute to the loss of impulse control. Therefore, changes in neurocircuitry involved in impulse control have significant implications for understanding addiction vulnerability. Literature reported that the onset of addictive disorders is mainly concentrated in the adolescence and young adulthood phases (Chambers et al., 2003). Thus, neuromaturation changes in frontal cortical and subcortical systems in adolescence may promote learning for adaptation to social roles, but may also confer them greater vulnerability to addictive behaviours.

Although scientific evidence supports a neurobiological basis for SUD, the link between the mechanisms underlying dysfunctional behaviours and biological systems is still unclear. As we better explain in Chap. 2, a recent study found that individual differences in personality traits, such as extraversion, neuroticism, and constraint, which implies intentional and volitional motor control, are related to the genetic profile that could lead high-risk individuals to develop an addiction disease (Belcher et al., 2014). Indeed, authors postulated that some personality traits underlying dimension of sensitivity to signals of punishment or reward, moderated by genes, interact dynamically with the environment to determine the degree of vulnerability or resilience to the development of SUD (Belcher et al., 2014).

Regarding the comparison between individuals with SUD and behavioural addictions, both groups reported a high rate of impulsiveness and sensation seeking on self-report scales and, in most cases, low on harm avoidance measures (Grant et al., 2010; Kim & Grant, 2001). In individuals with PG, impaired inhibition of motor responses (impulsivity) has been described, accounting for their poor inhibitory control over gambling habits, along with other impairment in sustained attention, or more commonly in executive functioning and cognitive control (Chowdhury et al., 2017).

In PG and IGD relative to healthy individuals, Fauth-Bühler and Mann (2017) observed loss of sensitivity, increased reactivity to relevant signals, increased impulsivity, and altered reward-based learning (Fauth-Bühler & Mann, 2017). Pathological

gamers have been found to prefer smaller immediate rewards over larger delayed compensations, overall displaying in the end more impulsive choices (Irvine et al., 2013).

Concerning individuals with IA, they have shown more impulsive behaviour than controls on the go/stop impulsivity paradigm (Cao et al., 2007), and more enhanced dysfunction in inhibitory control relative to the control group at the Stop Signal Test (Choi et al.,2013) (for a review, see Grant & Chamberlain, 2017).

In addition, impulsivity has been not only considered as a feature or a consequence of addictive behaviours but it has been included in the risk factors associated with PG and Excessive Smartphone use (Derevensky et al., 2019). The extensive role of impulsivity and the impairment related to the control of impulsive choices in behavioural addictions will be better explored in Chap. 2.

1.9 The Future Treatment Approach Based on Integrated Models: Neural Stimulation

Thus, all these data highlight the importance of an integrative model of addiction that takes into account the reward-bias system related to anomalous lateralized response in cortical activity (unbalance effect) and, at the same time, the possibility to induce by neuromodulation or neurostimulation an improvement of the symptomatology through a balancing of the cortical activity.

Based on this evidence, in recent years, interest has grown in non-pharmacological interventions in addiction disease, because pharmacological strategies are of limited effectiveness. The application of brain stimulation techniques as treatment of SUD could be applied for all addiction behaviours, including subjects at high-risk of dependence who could have vulnerability in the development of dysfunctional reward mechanisms and unbalance of PFC activity. The use of non-invasive and low-cost neuromodulation techniques is suggested, since they will have important implications in terms of social security, reducing costs of health expenditure, relapse prevention, improving the quality of care, treatment and prevention of addiction disease.

In recent years, interest has grown in the application of brain stimulation techniques as treatment of addiction, thanks to the use of non-invasive and low-cost neuromodulation, but also because pharmacological strategies are of limited effectiveness. These experimental techniques as treatment of addiction could be applied also for individuals at high risk of dependence who could have vulnerability in the development of dysfunctional reward mechanisms and unbalance of PFC activity. Specifically, brain stimulation is the use of electric or magnetic energy to improve brain function. It is applied for both research and treatment of psychiatric and neurological disorders, which do not always fully respond to conventional treatments (pharmacological or psychotherapeutic).

Stimulation with electrical or magnetic energy interacts with the neurons of the cortex, causing the release of neurotransmitters that can inhibit or excite specific cortical networks (Amiaz et al., 2009) and modulate the cortical activity. In particular, two techniques have been mainly tested in neuroscientific studies, such as the Transcranial Magnetic Stimulation (TMS) and the transcranial Direct Current Stimulation (tDCS). The TMS modulates the activity of the brain with magnetic pulses focused on a limited portion of the scalp by a coil (high frequency: excitatory; low frequency: inhibitory). Repeated sessions of TMS over the DLPFC were observed to reduce drug craving, drug-seeking and drug consumption, and relapse in nicotine addicts and CA (Amiaz et al., 2009; Camprodon et al., 2007); and to improve cognitive abilities in alcohol dependence (Del Felice et al., 2016). The tDCS can induce functional changes in the cerebral cortex. It consists of applying on the scalp two electrodes, one anode (excitatory) and one cathode (inhibitory), delivering a continuous current of low intensity that is not perceptible by the individuals, crossing the scalp and influencing neuronal functions. Literature showed that tDCS anodal stimulation over the right DLPFC induces a reduction in risky behaviour in CA (Gorini et al., 2014), induces decreased ACC activity after visualization of drug cues (Conti & Nakamura-Palacios, 2014), and reduction in nicotine, cocaine, and alcohol craving (Batista et al., 2015; Boggio et al., 2008; Fregni et al., 2008). These findings supported the hypothesis that excessive risk propensity in patients with addictions might be due to a hypoactivity of the right DLPFC and hyperactivity of the left DLPFC, as it was found in previous studies (Balconi et al., 2014c; Balconi & Finocchiaro, 2015).

1.10 Conclusions

In this first chapter, similarities and differences between old and new addictions have been described with a focus on EFs and reward mechanisms.

The behavioural parallels between SUD and new behavioural addictions (PG and IGD) encompassing neural responsiveness in specific brain areas (not limited to reward system structures), tolerance aspects, withdrawal, repeated ineffective attempts to avoid or stop playing, and impairment of normal functioning has been initially defined, starting from the diagnostic classification criteria. Interestingly, it emerges how in this framework the exploration of the role of the EFs in both behavioural and substance addiction appears limited, and it needs adjunctive clarifications.

Therefore, in this chapter, the impairment of EFs in SUD and behavioural addiction have been presented focusing mainly on decision making and metacognition processes, until the discussion of commonalities and differences for EF and neural circuits in "old" and "new" addiction. Reward sensitivity, decision-making impairment, and poor inhibitory control are three main features which can be observed at the neural level and that are shared by SUD and PG, and even

partially by IGD and IA, but the research literature appears less consistent on these latter and other behavioural disorders.

Besides the description of the involvement of the reward system at the neural level, reporting the evidence derived from neuroimaging studies in both SUD and behavioural addiction, the Cortical Unbalance Model has been here included to highlight the neurophysiological (EEG) and "attitude" effects' important roles as potential predisposing factors of this category of disorders. Indeed, individuals with a high-BAS trait, left hemispheric unbalance, and reduced levels of self-control (suggesting a possible deficit in brain inhibitory control brain networks) may be especially vulnerable to the development of SUD, or other addicted behaviours. Also, the commonalities in impulsivity and psychological trait have been anticipated here but will be further deepened in the following chapters.

To conclude, all these data highlight the importance of an integrative model of addiction that takes into account the EFs impairment, the reward-system neural correlates (including anomalous lateralized response in EEG cortical activity), and, at the same time, the possibility to implement new future treatment approach, including neuromodulation or neurostimulation techniques, aimed at empowering the brain functioning and improving individual's symptomatology.

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Chapter 2
Psychopathology of EFs

Davide Crivelli and Michela Balconi

2.1 Executive Functions: Conceptual Frame and Internal Structure

Executive functions (EF) can be generally described as a set of cognitive skills that lies at the core of higher cognition. Indeed, as reported in Chap. 1, they support top-down control and regulation of sensations, emotions, behaviour, and thoughts, and allow for flexible adaptation to the environment, self-monitoring and self-regulation, learning, complex reasoning, and strategic planning.

As such, integrity and efficiency of EF is associated to different achievements and aspects of human life, such as academic and professional attainments, relationship quality, and physical/mental health (Best et al., 2009; Bora et al., 2009; De Panfilis et al., 2013; Hall et al., 2006; Mesholam-Gately et al., 2009; Snyder, 2013; Valiente et al., 2013). The above-mentioned connection between EF, life skills, and psychophysical well-being points out the crucial role of such higher cognitive functions also as protective factors, moderators of quality of life, and precursors for effective global functioning. Consistently—as well as consequently—the alteration of EF following developmental disorders or acquired impairments typically connotes a wide range of neuropsychiatric pictures and dysfunctional conditions, among which learning disabilities (Toll et al., 2011), attention deficit/hyperactivity disorder (Petrovic & Castellanos, 2016), disorders of conduct (Rubia, 2011), autism

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spectrum disorder (O'Hearn et al., 2008), obsessive–compulsive disorder (Pietrefesa & Evans, 2007), depression and anxiety (Nelson et al., 2018; Shi et al., 2019), and substance use disorder (Ersche et al., 2012; Nigg et al., 2006).

The centrality of EF in both typical and atypical functioning and the pervasiveness of dysexecutive impairments across neurology and psychiatric conditions properly mirror initial remarks and models of their structure and neural basis. Namely, since its first definition, models of EF primarily derived from clinical observation of patients with prefrontal lesions (Luria, 1966), observations that highlighted the occurrence of a difficulty in strategically and intentionally regulating behaviour and cognitive processes, notwithstanding such basic cognitive processes were not affected. Notably, those very same clinical observations and reports justify the hierarchical structure that defines EF, according to which, prefrontal structures occupy the highest ranks in the hierarchy and exert their control over other cortical and subcortical structures, as well as neural networks. Yet, it is now known that such top-down connections are actually modulated by feedback loops, which create a complex circuit capable of fine-graded control over thought, sensations, perception, and behaviour. Furthermore, as underlined by Snyder et al. (2015), the functional association of different prefrontal areas with different EF components is made possible by the inclusion of such areas in complex networks, including regions and nodes that lie outside of the prefrontal cortex and, especially, subcortical and limbic structures.

2.1.1 "Hot" and "Cool" Subcomponents of EF

In particular, it was quite systematically demonstrated that EF skills can be classified as "hot" or "cool" based on the affective and motivational significance of the context, situation, task, or object they are applied to and based on their primary neurofunctional substrate—namely, a network centred on dorsal-lateral regions of the prefrontal cortex for cool EF and a network centred on ventral-medial regions of the prefrontal cortex for hot EF (Fonseca et al., 2012; Nejati et al., 2018; Zelazo & Carlson, 2012).

Notably, while the distinction between hot and cool EF is corroborated by vast experimental, clinical, and neurophysiological evidence, it is now accepted that cool EF plays a moderation role over hot EF and that tests and tasks typically used to assess executive control and higher cognition in motivationally-loaded contexts and to quantify impaired decision-making and executive control in addiction—such as the Iowa Gambling Task (Bechara et al., 1994), the less-is-more task (Carlson et al., 2005), or the Balloon Analogue Risk Task (Lejuez et al., 2002)—actually tap on both hot and cool EF skills (Manes et al., 2002; see Moriguchi & Shinohara, 2019). Consistently, according to Rolls functional model of ventral prefrontal areas (Rolls, 2004), what actually engages hot EF skills and related cortical substrates may not be the affective salience of a stimulus per se but, instead, the need to flexibly appraise and reappraise the motivational value of a salient stimulus during the

task, thus modulating approach and avoidance drives. And again, as underlined by Zelazo (2020), hot and cool EF do interact also for deliberate emotion regulation, where control over automatic approach–avoidance reactions and modulation of affective responses is commonly exerted via self-monitoring, reflection, decentring, distancing, and/or metacognitive practices (Bernstein et al., 2015; Kross et al., 2011; Travers-Hill et al., 2017). It is therefore not surprising that almost every clinical model concerning the psychopathology of EF and, in particular, models focused on neurocognitive, behavioural, and affective components of addiction points out the deeply interwoven relationship between self-regulation, stress-related, inhibitory, and higher cognitive control processes.

The unitary though multifaceted nature of EF is also well represented by the mostly diffused models of *unity/diversity* (Banich, 2009; Diamond, 2013; see Duncan et al., 1997; Miyake et al., 2000; Stuss, 2011), an account originally proposed by Teuber (1972). The core concept of such model is that specific processes, mechanisms, and skills constituting the EF are interconnected and correlated—and this stands also for contrasting hot and cool components—these being rooted in a common latent trait, but—at the same time—they also express different facets of higher cognition and quite specific subprocesses that can be assessed by using different neuropsychological tests or neurocognitive tasks.

2.2 Neurofunctional Correlates of EF: The Role of Prefrontal Hubs

According to the *unity/diversity model* by Miyake et al. (2000), EF rest on three main functional components—working memory (with a focus on information updating processes), shifting (as a component of cognitive flexibility), and inhibition—as well as a common general ability overarching these three components. Experimental and clinical evidence suggest that such internal structure can be observed across the life-span, from childhood to elderly age (Lehto et al., 2003; Miyake et al., 2000; Rose et al., 2011; Vaughan & Giovanello, 2010), though it seems to emerge starting from school age, since it was reported that preschool children might present a simpler monofactorial or bifactorial structure of EF skills (Miller et al., 2012; Wiebe et al., 2011).

A recent neuroimaging study elegantly investigated neurofunctional correlates of those three main EF components, controlling for task effects (Lemire-Rodger et al., 2019). Imaging data highlighted the role of dorsolateral prefrontal cortex (dlPFC), lateral parietal cortex, and bilateral insula in supporting working memory updating processes, while inhibition skills were associated with right lateral and medial PFC, bilateral inferior parietal lobules (IPL), and right middle and inferior temporal cortex, and, finally, shifting and cognitive flexibility processes were primarily supported by bilateral medial PFC, posterior cingulate cortex (PCC), precuneus, left IPL, lateral temporal cortex, and right thalamus.

Once again, the coordinating and supervising role of different prefrontal structures clearly emerges, further corroborating the vast amount of clinical data coming from lesion studies. In particular, clinical research in neurology and neuropsychology has systematically reported the association between different clinical manifestations of the dysexecutive syndrome and many behavioural symptoms with a variety of PFC lesions (Baddeley et al., 1997; Stuss, 2011; Tsuchida & Fellows, 2013), while also pointing out the concurrent effect of such lesions on the complex set of circuits connecting the PFC to other cortical and subcortical structures, such as the basal ganglia, the cerebellum, and the limbic system (Bonelli & Cummings, 2007; Fuster, 1997, 2001; Stuss & Benson, 1987). Such hierarchical organization in neurofunctional and clinical models of EF is consistent with neural and cognitive models of most complex functions of our mind, such as communication and language (Chomsky, 2002) or intentional action (Pacherie, 2008), and, as in those cases, accounts for the multiplicity of executive control facets and of related cognitive subroutines, while also accounting for top-down influence of higher processes and superordinate representations (e.g. intentions, goals, desires, self-beliefs, previous knowledge) over functional and dysfunctional behaviour.

Several studies have shown that specific portions of the PFC play a crucial role for attention regulation, goal setting and maintenance, top-down control of irrelevant information, modulation of salience, and behavioural inhibition (Banich, 2009; Dosenbach et al., 2008; Miller & Cohen, 2001), thus contributing to neurocognitive efficiency. Furthermore, it was shown that tDCS- and TMS-induced neurostimulation of the dlPFC, the core hub of the cognitive control network (i.e. a supervisory system including dlPFC, dorsal anterior cingulate cortex, and parietal cortices that regulate lower cognitive and emotional systems) may also, via the empowerment of executive control over emotion regulation mechanisms, positively affect anxiety and depressive symptomatology (Avissar et al., 2017; Balconi & Cobelli, 2014; Balconi & Ferrari, 2012, 2013; Ironside et al., 2019).

Besides dorsal and lateral portions of the PFC, the ventral-medial and orbitofrontal regions of the PFC and the anterior cingulate cortex (ACC) also play a crucial role in self-regulation and self-monitoring (Botvinick, 2007; Rolls, 2004). The ACC and inferior parts of the PFC, thanks to their connections with limbic and basal structures, act as a control hub for motivational and affective functions, thus contributing to: behavioural activation/inhibition and regulation of emotional reactivity; encoding conflict, errors, and motivational signals; responding to and learning from reinforcement contingencies (both punishments and rewards); and detecting of errors in behaviour or contextual feedbacks, thus being able to optimize performance and make future responses more efficient. Notably, despite the well-known role of ventromedial prefrontal cortex (vmPFC) in decision-making and self-regulation processes, the influence of motivational factors—namely, risk pressure—on such processes seems to mainly impact on ACC. Indeed, unlike the vmPFC, which primarily code for well-defined options and is mainly responsive to choices with determined values (Fellows, 2006; Hunt et al., 2012; Kolling et al., 2012), ACC activity seems to depend on the level of risk pressure and to be sensitive to changes in the value of different choices (Kolling et al., 2012, 2014; Quilodran et al., 2008).

The integrity of such structures and related networks is necessary to properly integrate and process alerting signals to direct brain responses towards salient stimuli, prioritize and manage action plans, and guide goal-directed behaviour.

2.3 EF in Psychopathology

As to date, underlined by many systematic reviews and meta-analysis, neurocognitive impairments and, in particular, EF deficits systematically pair with most psychopathological pictures (Buckholtz & Meyer-Lindenberg, 2012; Goschke, 2014; Nolen-Hoeksema & Watkins, 2011) and represent one of the most common transdiagnostic features across the lifespan (Millan et al., 2012; Snyder et al., 2015). On the neural level, McTeague et al. (2016, 2017) have, for example, recently pointed out that a functional alteration in correspondence of frontal, parietal, cingulate, and/or insular structures constituting the well-known central executive network (Menon, 2011) or multiple-demand network (Duncan, 2010, 2013) are typically observed across major psychiatric disorders—as a sort of common transdiagnostic pattern—and that structures that are part also of the salience network, such as the above-cited ACC and insula, often present reduced grey matter volume in different psychopathologies, predicting weaker neurocognitive performance in patients.

Those evidence contributed to the definition and corroboration of the triple network model of psychopathology (Menon, 2011). According to such transdiagnostic neurofunctional model, the investigation of atypical development or functioning of three main large-scale networks in the human brain—the default mode network (DMN), the central executive network (CEN), and the salience network (SN)—provides valuable information to explain and qualify clinical traits that connote major psychiatric and neurological disorders, and alterations in engagement and disengagement of those three neural networks play a significant role in shaping cognitive-affective-behavioural symptomatology. Furthermore, the model predicts that dysfunctions in one core network can impact the other two networks, with clinical manifestations that may transcend the primary deficit. As an example, a dysfunctionally heightened coupling of DMN and SN activity has been observed in patients presenting mood disorders, namely depression, and was associated to rumination and inability to disengage from internal mental processes and direct cognitive resources to significant external stimuli (Berman et al., 2011). Also, it was shown that patients with schizophrenia show structural and functional deficits undermining all the three networks (Palaniyappan et al., 2011), with severe cascading consequences in terms of the regulation and allocation of attention and cognitive resources and engagement of supramodal fronto-parietal and fronto-temporal systems supporting higher-order cognition, self-consciousness, and self-regulation. In dementia, alterations of SN-DMN connectivity are linked to unique patterns of social, affective, and episodic memory deficits (Zhou et al., 2010). And again, an alteration of cortical and/or subcortical nodes of the executive control or salience networks (Fox & Raichle, 2007; Seeley et al., 2007) is typically associated with the wide

range of impairments of higher cognition and cognitive-affective regulation skills that are commonly found in major psychopathologies. As suggested by Menon (2011), significant levels of anxiety or neuroticism might, as an example, follow dysfunctionally enhanced salience detection and misattribution of arousal and affective significance to mundane events due to hyperactivity of specific nodes of the salience network, such as the amygdala. Similarly, specific drug paraphernalia or specific contextual cues (e.g. the sign of a betting shop) may be uniquely salient to individuals presenting substance use disorder or behavioural addiction, due to altered saliency filtering, detection, and mapping, as well as dysfunctional reward responsiveness and a concurrent impairment of self-control and inhibition.

In addition to the above-introduced neurofunctional evidence, neurocognitive efficiency also proved to predict various clinical outcomes in adult psychiatry patients (see Fig. 2.1)—such as long-term functional recovery (Jaeger et al., 2007), quality of life (Cotrena et al., 2016), and social/occupational functioning (O'Donnell et al., 2017)—and to contribute to the concurrent or proximal exacerbation of psychopathological traits, autonomy, and overall functioning in children and adolescents (Han et al., 2016; Khurana et al., 2015; Lee et al., 2013). More specifically, it was shown that weaker executive functioning is correlated to rumination (De Lissnyder et al., 2012; Demeyer et al., 2012; Whitmer & Banich, 2007), worry (Crowe et al., 2007; Snyder et al., 2014), and dysfunctional emotion regulation strategies (Andreotti et al., 2013; McRae et al., 2012). And again, poor executive control was associated to greater behavioural disinhibition (Friedman et al., 2011; Young et al., 2009), which acts as a risk factor underlying many externalizing behavioural pictures, such as *attention deficit* hyperactivity disorder (ADHD), conduct disorder, substance use disorder (SUD), and heightened novelty-seeking and risk-taking. Consistently, a recent study based on a network analysis of clinical symptoms in a sample of 849 adolescents (Madole et al., 2019) highlighted the role of EF by showing that, when added to the symptom network, the selected EF measure showed the largest number of connections to other nodes of the network (i.e. symptoms), thus standing out as the most central node of the network, while

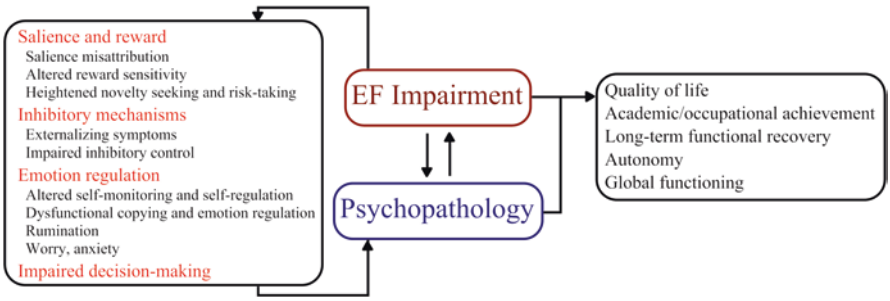

Fig. 2.1 Synoptic schema of the relationship between executive functions (EF) impairments and psychopathology, with a focus on primary predicted clinical outcomes and concurrent clinical signs or psychopathological traits

self-reported emotional control only reached the 11th position in terms of connections and centrality.

The pervasiveness and transdiagnostic nature of EF and, more generally, neurocognitive deficits across different psychopathological conditions is further suggested by the limited evidence for peculiar neurocognitive differences between specific psychiatric disorders, contrasting with the plethora of empirical observations concerning differences with respect to healthy control subjects. This very same remark is stressed in a recent and large observational study aimed at extending the literature on cognitive functioning and comorbidity across different neuropsychiatric conditions (Doyle et al., 2018). Four hundred and eighty-six youth referred for neuropsychiatric evaluation were enrolled in the Longitudinal Study of Genetic Influences on Cognition and also underwent standardized assessment of intelligence and general ability, reaction time variability, and executive functions. Participants presented non-comorbid forms of ADHD, mood disorders, autism spectrum disorder (ASD), and psychosis. All of them showed neurocognitive deficits, without significant differences between the diagnostic categories. Moreover, findings suggested that common beliefs about disorder-specific deficits, such as altered inhibitory mechanisms in ADHD, were not systematically supported by data, since no particular cognitive impairment was specific to any disorder.

As posited by Zelazo (2020), the systematic occurrence of EF impairments across different psychopathological conditions over the entire lifespan suggests that atypical development or acquired dysfunctions of EF might be a common consequence of many different kinds of developmental perturbation linked, among others, to genetic, environmental, epigenetic, cognitive, affective, and social factors. Complex interactions between those very same factors might, in addition, justify the variability of clinical manifestations concerning executive control and higher cognition in different patients. Indeed, while the presence of EF dysfunction can be deemed, logically speaking, as a transdiagnostic component of psychopathology, the severity and functional characterization of such dysfunctions are connoted by remarkable variability. Namely, prevalence estimates of clinically relevant neurocognitive disorders in association to different psychiatric disorders range between 27 and 93% for the bipolar disorder (Godard et al., 2011; Gualtieri & Morgan, 2008; Reichenberg et al., 2009), 23–81% for depression (Godard et al., 2011; Gu et al., 2016; Gualtieri & Morgan, 2008), 55–84% for schizophrenia spectrum disorders (Reichenberg et al., 2009), 18–50% for anxiety pictures (Gualtieri & Morgan, 2008), and 50–89% for ADHD (Kofler et al., 2019; Lambek et al., 2011). Relevant for the present discussion, comparably variable ranges were reported for mild neurocognitive disorder induced by substances or drugs—30–70%—and major neurocognitive disorder—0.7–35% of the reference clinical population (Bruijnen et al., 2019; Fernández-Serrano et al., 2010; Marín-Navarrete et al., 2018; Toledo-Fernández et al., 2016).

According to a neurodevelopmental model of psychopathology, many factors and life events may, then, shape the yet strong relationship between executive impairments and psychopathology, though the direction, origin, and evolution of the causal relation between those clinical constructs have not been fully clarified nor

investigated. It is, indeed, still unknown if deficits in executive control and self-regulation precede, follow, or simply correlate with psychopathology. And yet, understanding whether dysexecutive manifestations are a potential risk factor for developing psychopathology, or conversely are a consequence of psychopathology, or systematically co-occur with psychopathology—these being, for example, both associated or caused by a third factor—would be an invaluable advantage in devising effective protocols for assessment, monitoring, prevention, and intervention.

To conclude, as stressed by Kavanaugh et al. (2020), despite the broadly-recognized relevance of neurocognitive skills, no proper nosology of executive and higher-cognition deficits in psychopathology have been developed and intervention protocols that specifically target them are very scant and understudied. A unified model for classifying and recognizing neurocognitive impairments in psychopathology is needed to improve the quality of assessment and to implement care protocols that respect the complexity of such clinical pictures. While such global goal is far and yet to be reached, the next section focuses on addiction and substance-related disorders, discussing the relationship between EF alterations, impaired reward sensitivity, inhibitory control, and such clinical conditions in the light of the neurofunctional models of addiction behaviour.

2.4 Psychopathology of EF in Addiction

The main neural circuits that appear to be involved in substance abuse and in the implementation of dysfunctional behaviours are the mesostriatocortical system, the alarm system, including the amygdala, and the prefrontal executive network (Koob & Volkow, 2016; Volkow et al., 2013). The combination of an altered prefrontal executive control activity and the dysfunctional adaptation of the reward system is thought to form the basis of the pathological drive toward the substance of abuse, but neuroscientific evidence suggests that similar neurofunctional alterations could also mediate behavioural addictions (e.g. pathological gambling, internet addiction, food addictions), characterized by salience misattribution, dysfunctional reward mechanisms, deficits in cognitive control, and impaired decision-making processes (Balconi et al., 2017; Balconi & Finocchiaro, 2016b; Marazziti et al., 2015; Potenza, 2008; Wang et al., 2002; Yamamoto et al., 2014). At the same time, the chronicization of substance use or of the implementation of dysfunctional behaviours induces structural and functional changes in prefrontal regions (Goldstein & Volkow, 2011; Koob & Volkow, 2016; Volkow et al., 2013). Consistently, clinical and neuroimaging studies showed that patients with addiction often present a variety of neuropsychological deficits shared by patients with frontal lesions (Bechara et al., 2000), including a deficit of inhibitory control and decision making (Balconi et al., 2014a; Verdejo-García & Pérez-García, 2007).

Such form of executive impairment—together with the alteration of memory, reward regulation, and decision-making processes—also helps in understanding the issue of relapses. There is evidence, for example, in cocaine users, that prefrontal

self-regulation mechanisms are deactivated following exposure to stressful stimuli and unpleasant emotions, while the reward system (mesolimbic area) is activated under stress, inducing craving (Breese et al., 2005; Volkow & Morales, 2015). A dysregulated stress system can therefore induce craving even after years and, due to the reduced inhibitory control, facilitate the occurrence of relapses and abuse behaviours.

As a first conclusion, the integrated contribution of inhibitory control deficits, of the dysfunctional alteration of reward mechanisms, and of the enhanced sensitivity of alarm systems to the definition of the clinical manifestations of behavioural addiction or substance use disorder is well represented by the integrative model of the cortical imbalance in addiction (Finocchiaro & Balconi, 2017). Within the framework of that model, the anomalous reactivity to rewards associated with a substance or a peculiar conduct, the impairment of inhibitory mechanisms, and the marked tendency to impulsiveness shown by some individuals who present addiction, as well as the deficits in decision-making processes and the altered sensitivity to aversive stimuli, would be attributable to an imbalance in the activation of two prefrontal affective-motivational systems that regulate approach and avoidance behaviours (respectively, the behavioural activation system and the behavioural inhibition system; Gray, 1981). In particular, a functional asymmetry in favour of the behavioural activation system was observed in both behavioural addiction (Balconi et al., 2014b, 2017) and substances use disorders (Balconi & Finocchiaro, 2015), associated with peculiar sensitivity to rewards and immediate gratifications and lack of impulse control.

2.4.1 Bridging the Gap: Neurocognitive Models of Addiction

The complexity of the clinical picture associated with addiction and substance use disorders and, in particular, the articulated interaction between psychological, physiological, and neurocognitive factors is well represented by recent neurobiological hypotheses that describe the dynamics and the evolution of addiction and its behavioural manifestations, also taking into account the role of associated neurocognitive impairments (Goldstein & Volkow, 2011; Koob & Volkow, 2016).

These hypotheses conceptualize addiction as a progressively worsening dysfunctional cycle consisting of three phases—binge/intoxication, abstinence/negative emotions, and worry/anticipation—which involve, in line with the explanatory framework offered by the integrative model of cortical imbalance in addiction (Balconi & Finocchiaro, 2016a), an impairment of both response inhibition skills and salience attribution processes (impaired Response Inhibition and Salience Attribution—iRISA syndrome; Goldstein & Volkow, 2011). Impairment of impulse control and of salience attribution processes directed to internal and environmental stimuli would in turn derive—as previously discussed—from structural and functional alterations of a cortico-subcortical system that includes, as its main hubs, different structures in the prefrontal cortex.

The binge/intoxication phase refers to the consumption of the substance or the implementation of maladaptive behaviour, and is associated with high concentrations of dopamine in the limbic areas, particularly in the nucleus accumbens. Compulsive consumption is the result of repeated experiences with the substance or conduct of abuse that alter both the reward circuit and the prefrontal areas of salience attribution, inhibitory control, and emotional self-regulation. Executive control over the attribution of salience is essential for the efficiency of decision-making processes, for the maintenance of goal-oriented behaviours, and for the flexibility of regulation and learning of stimulus-response associations. Due to these modifications, an intense desire for the substance (craving) can induce the impulsive search for the substance and the massive and acritical use of the substance (binge).

In the phase of abstinence/negative emotions, the repeated use of the substance or the recurrence of dysfunctional behaviour alter the ability to experience pleasure through natural rewards. At the same time, changes in the extended amygdalar system alter the individual's responsiveness to stress and favour the emergence of negative emotions. In this phase, the individual engages in substance use or dysfunctional behaviours not just to seek pleasure but, rather, to escape negative emotions.

In the worry/anticipation phase, the repeated consumption of the substance or the implementation of addiction behaviour induce, finally, a decrease in dopamine levels also in the prefrontal areas, which dramatically compromises the ability to attribute salience to stimuli from the environment, to self-regulate, to make decisions, to select and flexibly engage in adaptive behaviour, and to monitor automatic responses and mistakes. It follows, in a scenario of impaired higher cognitive abilities, the inability to stop using the substance or implementing the dysfunctional behaviour despite the awareness of its negative effects.

The crucial role of the prefrontal cortex for higher executive functions and the presence of an impairment of specific prefrontal areas and related cortico-subcortical circuits in case of addiction are also highlighted by several recent neuroimaging studies (Goldstein & Volkow, 2011; Kalivas & Volkow, 2005; Koob & Volkow, 2016; Volkow et al., 2004). These studies have shown how the increase in dopamine during the intoxication and craving phases, as well as the decrease in dopamine that accompanies chronic drug use, also affect the orbitofrontal cortex and the anterior cingulate gyrus (Goldstein & Volkow, 2011; Koob & Volkow, 2016) and that the same orbitofrontal glutamatergic projections at the nucleus accumbens are altered (Kalivas & Volkow, 2005).

Overall, a series of alterations were found in the prefrontal regions, and in particular in the mesocorticolimbic dopaminergic circuits and in the corticostriatal glutamatergic circuits, which can compromise various executive functions, such as inhibitory control, attribution of salience to stimuli, decision making and goal-oriented behaviour, flexibility in selecting and initiating an action, inverted learning, and error tracking (Bechara, 2005; Izquierdo & Jentsch, 2012; Koob & Volkow, 2016; Volkow et al., 2004), with a consequent difficulty, for example, in deciding to discontinue the use of the substance or the implementation of dysfunctional behaviours, as well as in persisting in this decision.

In addition, alterations of the insular regions contribute to impair self-awareness, i.e. the ability to recognize and reflexively process one's sensations and mental objects, such as emotions, feelings, desires, beliefs, and representations of one's abilities (Goldstein & Volkow, 2011). These alterations in addiction contribute to the development and maintenance of compulsive seeking and consumption behaviours concerning the substance or the conduct of abuse and, at the same time, they make particularly difficult to voluntarily stop the practice, despite the person knowing and experiencing the catastrophic consequences of addiction. The ability to develop conscious decision-making strategies and the broader metacognitive functions associated with them also appear to be partially compromised, as happens in pathologies that involve similar deficits in the domain of decision-making (Angioletti et al., 2019, 2020; Balconi et al., 2018).

2.5 Conclusions

This chapter was aimed at introducing the deep link between EF and psychopathology. Pursuing such goal, we have firstly outlined the main conceptual components of EF, then presented their neurofunctional correlates (with a specific focus on prefrontal structures and primary neural networks), and finally discussed the complex relationship between EF, neurocognitive deficits, and clinical manifestation of psychopathology. In particular, while pointing out the transdiagnostic role of neurocognitive impairments, we have focused on altered executive control, behavioural inhibition, and reward sensitivity in models of substance-related and behavioural addiction.

As a final note, however, it is worth reminding that, as posited by Kavanaugh et al. (2020), no systematic nosology of executive and higher-cognition deficits in psychopathology have yet been developed, notwithstanding their well-known and broadly-recognized role in shaping cognitive-affective-behavioural symptomatology in addiction and other major neuropsychiatric pictures.

Plausibly, such current lack partly derives from limitations inherent in available literature. Indeed, neuropsychological tests commonly used to investigate EF and their neurofunctional correlates mostly tap on multiple aspects of EF as well as non-EF processes (e.g. mnestic retrieval, visual-spatial cognition). Therefore, while being informative when used to assess individuals presenting moderate/severe executive impairments, they might not optimally capture milder difficulties or answer fine-grained research questions on the internal structure of different EF skills, their specific neurofunctional correlates, or peculiar associations with different psychopathological pictures.

Those weak points have been specifically pointed out by available evidence and, especially, clinical practice concerning the investigation of EF in the care and assistance services for addiction. Despite being recognized as a crucial step of the diagnostic process, neurocognitive assessment of executive dysfunctions is typically underrepresented in the routine general practice in drug assistance/treatment

services, partly due to the lack of suitable and informative screening tools. The development of novel instruments to reliably outline the profile of strong and weak points in executive control and higher-cognition skills of individuals presenting old and new addictions is a current need for research and clinical practice and a challenge for the implementation of effective assessment and intervention programs.

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Chapter 3
The Assessment of Executive Functions: A New Neuropsychological Tool for Addiction

Michela Balconi and Davide Crivelli

3.1 Neurocognitive Deficits in Addiction

Given the severity and pervasiveness of the neurophysiological anomalies that result from the repeated consumption of substances or the systematic implementation of dysfunctional behaviours, it is not surprising that addiction pictures are often connoted by neurocognitive deficits especially affecting higher cognition, as documented by numerous studies focused in the use of different types of psychoactive substances and behavioural addiction profile (Antons et al., 2020; Brand et al., 2019; Fernández-Serrano et al., 2011; Yücel et al., 2007).

In particular, as we have shown in Chap. 1, alterations of the mesocorticolimbic dopaminergic circuits and of the corticostriatal glutamatergic circuits in prefrontal regions compromise various executive functions such as inhibitory control, attribution of salience to stimuli, decision-making and goal-oriented behaviour, flexibility in selecting and initiating an action, inverted learning, and error tracking (Antons et al., 2020; Bechara, 2005; Koob & Volkow, 2016), making it more difficult to decide to stop using the substance of abuse or enacting dysfunctional behaviours, as well as to persist in this decision. The ability to develop conscious decision-making strategies and the efficiency of metacognition also appear to be partially compromised, as happens in pathologies that involve similar deficits in neural circuits that foster decision-making processes (Angioletti et al., 2019, 2020; Balconi et al., 2018). Structural and functional alterations, then, contribute to the exacerbation of

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states of malaise, worsen conditions of psycho-physical frailty, and aggravate the severity of the general clinical picture.

As for the cognitive domain, the functions that show the greatest vulnerability are attention regulation, memory, executive functions (EF)—in particular inhibitory control, working memory, decision making, cognitive flexibility, and strategic orientation of cognitive resources—and emotion regulation skills (Antons et al., 2020; Gould, 2010). Furthermore, while the impairment of the "addiction circuit"—which includes parts of the reward, learning, and memory circuits and cortical structures involved in decision-making and inhibitory control—entails a set of generalized deficits transversal to different addiction pictures, it was shown that specific functions and cognitive processes may be more or less compromised depending on the substance of abuse and other parameters such as the duration of abstinence (Fernández-Serrano et al., 2011).

Specifically, notwithstanding the variability in clinical observations and inconsistencies in empirical findings, the most consolidated data suggest that persistent use of psychostimulants (cocaine and MDMA) affects, in particular, cognitive flexibility, working memory, inhibitory control and impulsivity, and regulation of affects, whereas the systematic use of opioids mainly affects decision-making processes and the efficiency of attention regulation, besides—again—working memory and cognitive flexibility, on decision-making abilities and on the efficiency of divided attention.

Conversely, currently available literature exploring cognitive deficits associated to behavioural addiction mostly highlight a shared impairment of inhibitory and executive control (attention regulation, inhibition, decision making, working memory) that, starting from cue-reactivity and altered sensitivity to specific stimuli of interest, affect the generalized ability of impulse control (Antons et al., 2020; Brand et al., 2019; Ioannidis et al., 2019; van Timmeren et al., 2018). Yet, it has to be acknowledged that such literature is still in its first moves and, though promising, had just began to systematically explore potential differences in the profile of neurocognitive and neurobiological alterations that pair with different categories of behavioural addiction (e.g. problematic internet use, gaming disorder, pathological gambling, compulsive buying disorder).

Despite the methodological efforts, it seems clear that the identification of the relationships between models of abuse, addiction-related neurofunctional alterations, and specific patterns of impairment of neurocognitive functions, with particular reference to EF, continues to be a complex and almost unsolved problem, likely due to the multiplicity of factors that affect those relationships. That underlines the clinical and methodological need for new assessment tools capable of detecting, qualifying, and quantifying the alteration of higher cognitive functions in patients who have developed addiction, in order to rapidly sketch an effective definition of their cognitive profile and of specific deficits and impairments.

3.2 Tools for Assessing EF in Addiction

In most of the cases and clinical contexts, cognitive and executive deficits shown by patients who present to psychiatric emergency or addiction assistance/treatment services are typically assessed via basic screening tools or short assessment batteries such as the Mini Mental State Examination (MMSE; Folstein et al., 1975), the Neurobehavioral Cognitive Status Exam (NCSE; Marcotte et al., 1997), the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004), the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), the Neuropsychological Assessment Battery – Screening Module (NAB-SM; Grohman & Fals-Stewart, 2004), and the Addenbrooke's Cognitive Examination – Revised (ACE-R; Mioshi et al., 2006).

Given the advantage of short administration and correction times (from 30 to 45 min) and the possibility to quickly outline global functioning profile, short cognitive batteries are commonly preferred to exhaustive neuropsychological assessment procedures. Again, further alternatives are neuropsychological screening tools focused on frontal functions or originally devised to assess dysexecutive syndrome in neurology patients, such as the Frontal Assessment Battery (Cunha et al., 2010; D'Onofrio et al., 2018; Dubois et al., 2000; Floris et al., 2012).

Neurology patients suffering from frontal lesions or dysfunctions, indeed, show behavioural disorders—such as impulsivity, altered self-awareness, and vulnerability to rewards—and cognitive impairments shown even by people who developed addiction – namely, difficulties in attention regulation, processing speed, and episodic memory. However, these and other tools built to detect executive deficits in the case of clinical pictures other than addiction (e.g. neurodegenerative disorders, schizophrenia, multiple sclerosis, HIV-associated dementia, etc.), may not be optimal when used to screen different clinical populations. This becomes even more relevant when the target population, as in the case of people presenting substance-related or behavioural addiction, differ from the original validation cohorts in terms of personal features other than the primary diagnostic profile, such as the age range. Yet, some brief assessment tools have been tested for feasibility and usability even in cases of substance use disorder and showed an interesting potential – namely, the NAB-SM (Cannizzaro et al., 2014; Grohman & Fals-Stewart, 2004) and the MoCA (Bruijnen et al., 2019; Copersino et al., 2009).

The Screening Module of the Neuropsychological Assessment Battery (NAB-SM) allows for a relatively brief assessment of five core cognitive domains: attention, language, memory, visual-spatial skills, and EF, providing also an overall functioning index. The NAB-SM has been validated as a screening tool in subjects with substance use disorder (Copersino et al., 2009; Grohman & Fals-Stewart, 2004) and, specifically, with people presenting cocaine addiction (Cannizzaro et al., 2014). Still, this tool might be overly broad, thus providing information on cognitive functions that are not at the core of addiction-related neurocognitive disorders, while lacking focused investigation of functions that are typically affected by addiction, such as inhibitory control.

The focus on EF is more peculiar of another screening tool that has been borrowed by neurology to psychiatric practice and tested with people showing substance use disorder (Bruijnen et al., 2019; Copersino et al., 2009): the Montreal Cognitive Assessment battery. The MoCA includes specific subtests for verbal memory, visuospatial skills, verbal and non-verbal EF, attention, working memory, language, and temporal-spatial orientation. Yet, it has to be acknowledged that memory and orientation subtests have a considerable weight compared to those that evaluate EF, therefore the sensitivity of the MoCA and its ability to identify profiles with prevalent executive deficits may not be optimal. Furthermore, from a qualitative point of view, it might be suggested that the subtests used to assess set-shifting and attention regulation skills are presumably too simple for the typical population of subjects who present to care and assistance services due to addiction.

3.3 Why a New Neuropsychological Battery for Screening of EF in Addiction

Available evidence and, especially, clinical practice, however, point out the inadequacy of the assessment or screening methods for EF currently used in the care and assistance services. In addition, in line with prevalence estimates, common field experience highlights that, in most cases that present themselves independently to assistance services seeking treatment for addiction disorders, the severity of neurocognitive disorders is mild and that peculiar deficits are not adequately detectable and quantifiable via general screening tools that were originally conceived for the evaluation of global cognitive impairment in neurological patients or cognitive decline in old age. Indeed, while those tools have shown good validity and accuracy for the detection of serious impairments, it was suggested that they are not fully apt for the identification and quantification of milder executive deficits (Bruijnen et al., 2019; Copersino et al., 2009), which, nevertheless, can have a significant impact on everyday activities and personal autonomy (e.g. by increasing the amount of cognitive resources required by routine activities due to the enlarged need for constant conscious monitoring).

During the diagnostic process (including a clinical interview with the patient and his family), it is therefore important to be able to effectively discriminate the nature of executive deficits and to identify risk factors and critical needs in the earliest stages. This would allow defining the most appropriate therapeutic plan for the patient, possibly planning a parallel cognitive rehabilitation phase. Such impairments or executive dysfunctions could, in fact, compromise the recovery programs and, above all, the patient's autonomy and sense of efficacy in the activities of daily life.

The neurocognitive assessment of executive dysfunctions associated with addiction pictures represents an element of the diagnostic process that is as fundamental as it is currently underrepresented in the routine general assessment practice in drug

assistance/treatment services. The lack of suitable tools for the neurocognitive assessment of executive dysfunctions associated with addiction pictures and specific training of clinical staff has largely contributed to that scenario.

We have, therefore, designed and tested a novel brief neurocognitive screening battery to meet those clinical, methodological, and practical needs. In designing and developing such novel tool, we started from practice and field experience by mapping cognitive assessment procedures and neuropsychological assessment tools that were most commonly used in drug assistance/treatment services, with a focus on the national context. Such field observations were then integrated with the critical analysis of the national and international literature on the subject, with particular focus on neuropsychological tests used for the evaluation of executive deficits associated with addiction. Those first steps provided valuable information that guided the subsequent phase of review of existing measures and design of novel tests included in the battery. The first version of the new screening battery underwent, then, pilot testing with a clinical cohort ($N = 30$ patients diagnosed with substance use disorder) to assess its efficiency and usability. Finally, taking into account the observations that emerged during conception phases and, above all, from pilot testing, the final version of the battery was created and subjected to validation with both control and clinical normative samples.

The neurocognitive battery—named Battery for Executive Functions in Addiction (BFE-A)—consists of seven subtests and includes measures dedicated to short- and long-term verbal memory, working memory, cognitive flexibility (with both verbal and non-verbal materials), focused attention, attention regulation and suppression of interference and inhibitory control (see Fig. 3.1). The BFE-A allows for outlining a general profile of the alterations of EF associated with addiction pictures. In addition, the calculation of specific performance indicators for the individual subtests allows to compare inter-test performance, as well as to identify strong and weak points in individual profiles, providing relevant information for planning targeted diagnostic investigations or personalized empowerment/rehabilitation interventions that take into account the patient's potential and specific needs.

The structure of the BFE-A includes both digitized neuropsychological tests and computerized neurocognitive tasks. The choice to implement such different methods for assessment originates from methodological and clinical reasons. Digitized

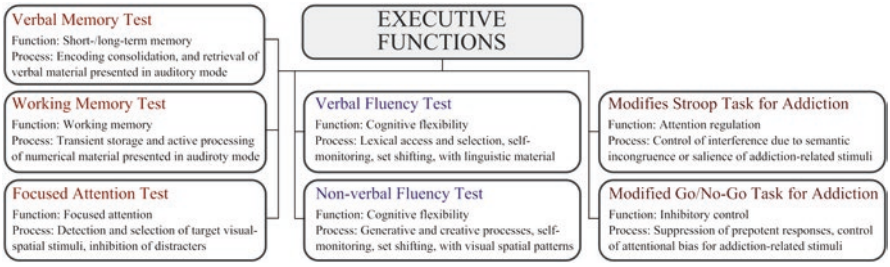

Fig. 3.1 Global structure of the Battery for Executive Functions in Addiction (BFE-A) with a focus on specific subtests and their functional correlates

testing and computerized performance measures, in particular, are characterized by a high level of control over the procedures of administration and execution of the test, and by remarkable precision in the presentation of stimuli. These peculiar properties are particularly useful in assessing moderate or mild cognitive impairment and increase the sensitivity of the assessment, thus allowing for a finer-grained picture of examinee's difficulties and residual abilities. Such greater sensitivity and discriminating capacity, even in case of milder impairment, becomes peculiarly relevant when applied to screen attention regulation skills and the efficiency of interference inhibition and cognitive control mechanisms. The consequences on behaviour and everyday life of minor alterations of those essential executive skills may, in fact, be hidden by compensation mechanisms, making them more difficult to identify via traditional cognitive tests.

3.4 Potential Applications: Salience and Innovativeness of the BFE-A

In its entirety, the above-presented BFE-A was built to assess, in a short time, the degree of impairment of high-order EF often observed in people who have developed substance-related or behavioural addiction disorders. The set of tests and tasks that constitutes the BFE-A was selected based on their relevance, as highlighted by empirical literature, and their diagnostic potential, as highlighted by available psychometric and clinical evidence. In the scenario of cognitive assessment practices, the use of a screening battery created ad hoc for the target clinical population—possibly followed, if needed, by second-level diagnostic investigations—constitute, indeed, a good compromise between the accuracy of a complete evaluation and the specificity of an assessment that is completely tailored on the individual patient and that, therefore, may require remarkable clinical experience to be properly set up.

Given the interest in creating a tool that could be efficiently administered in different clinical contexts and in services dedicated to the treatment and diagnosis of addiction pictures, the BFE-A was developed in compliance with the following principles:

- *Informativity*: ability to provide an overall profile of integrity of the examinee's EF and higher cognitive skills that could then possibly be complemented by second-level neuropsychological assessment, thus optimizing the resources dedicated to assessment procedures.
- *Psychodiagnostic value and clinical relevance*: optimal coverage of executive deficits associated with substance-related and behavioural addiction, as well as ability to provide information related to peculiar executive and higher cognitive functions known for their impairment in different addiction pictures.
- *Modularity*: possibility of using the tests of the BFE-A also as independent tests or of creating subsets of tests for specific diagnostic investigations, in addition to

the use of the BFE-A as a unitary tool for screening the executive functioning of the examinee.
– *Clinical usability*: rapid administration and correction times, as well as selection of materials and methods of administration that could be easily implemented and are simple to use in real-life clinical settings.

In particular, the intrinsic modularity and flexibility of the BFE-A allows outlining a first general profile of executive functioning in the examinee and, at the same time, to get specific pieces of information concerning strengths and weaknesses across explored cognitive domains. Furthermore, each subtest has been associated to performance and error indices that are both functionally and metrically comparable. That allows the examiner to outline intra-individual comparisons between the investigated functions, to draw parallels between the examinee's performances at the various subtests, and to identify specific effects of an implemented treatment protocol by weighing them transversely to the investigated cognitive domains, thus providing valuable hints for the optimization or efficiency testing of different care and assistance plans.

3.5 Presentation of an Empirical Validation Study

To sum up, the above-presented BFE-A was developed to try and answer clinical and methodological needs for a usable, valid, and brief screening tool, able to properly sketch a profile of residual skills and weaknesses concerning higher cognition and EF in substance-related and/or behavioural addiction. We will now briefly present the outcomes of the empirical validation study aimed at testing the feasibility, informativity, and robustness of the novel neurocognitive screening battery.

A total of 207 volunteers were enrolled by the Research Unit in Affective and Social Neuroscience of the Catholic University of the Sacred Heart of Milan and by the Canzio Drug Addiction Service of the ASST Fatebenefratelli-Sacco in Milan, with the additional support of the Alcoholic and Double Diagnosis Community of Castelfranco Veneto (TV). The total sample was divided into a clinical normative cohort constituted by 151 patients diagnosed with substance-use disorder and a control normative cohort constituted by 56 healthy volunteers. All of enrolled participants provided their informed consent for participation in the validation study, as well as for storage and treatment of related data. The project and related experimental procedures have been reviewed and approved by the relevant Ethics Committee, and comply with the rules and standards of the Declaration of Helsinki and its subsequent revisions.

All of participants included in the clinical cohort were diagnosed with substance-use disorder (diagnostic criteria by DSM-5; APA, 2013) and were involved in diagnostic and/or supportive programs by the above-mentioned drug assistance/treatment centres. Patients with secondary/concurrent diagnosis of neurological conditions or previous neurological clinical history were excluded from enrolment,

as well as participants who reported clinical instability in the 48 h prior to assessment session. In addition, volunteers with neurological or psychiatric clinical history, experience of recreational use of psychoactive substances (except alcohol), or first-degree relationship, professional, or volunteering experience with individuals who have been diagnosed with substance-use disorders were excluded from the control normative cohort so to prevent potential confounds.

The age range of enrolled participants was 18–60 years (M = 40.10 years; SD = 11.39), while their level of education varied between 4 and 22 years (M = 13.37 years; SD = 3.59). The sample was primarily constituted by males (males = 134; females = 73) mainly due to gender differences in the clinical cohort, which mirror commonly reported empirical and clinical observations concerning the prevalence distribution of addiction pictures.

The BFE-A has been administered by licensed psychologists trained in psychodiagnostic and neuropsychological testing in a single session. The complete assessment procedure lasted, on average, about 45 min. Scoring of participants' performance at the battery subtests was performed by the expert examiners and then checked by a second expert in neuropsychological testing, acting as additional blinded judge.

Performance data for each subtest of the BFE-A were, then, analysed to investigate the validity, reliability, and clinical potential of the tool. A first set of statistical analyses, which will be here briefly reported, focused on between-group comparisons in order to test for the capacity of the BFE-A to highlight significant differences between the performance of the control and clinical cohorts. Specifically, behavioural measures of performance were analysed via independent-samples t-tests ($\alpha = 0.05$) including Group (Control vs. Clinical) as the main factor. Finally, the size of significant effects was estimated via Cohen's d values to better appraise the relevance of observed between-group differences. Effect sizes have been deemed as small, medium, or large in agreement with Cohen's norms (1988).

Statistical analyses consistently showed worse cognitive performance in patients diagnosed with substance use disorder compared to healthy controls, both at neuropsychological tests of cognitive flexibility, focused attention, verbal memory, and working memory, and at neurocognitive tasks tapping on the efficiency of attention regulation, control of interference, and behavioural inhibition skills. Such scenario hints, in line with available clinical studies and observations concerning neurocognitive sequelae of addiction pictures, at the presence of a generalized impairment of regulatory mechanisms involved in orientation of attention/cognitive resources, inhibition of behaviour, and task-irrelevant information, as well as information processing and consolidation. Notably, the outcome of inferential statistics becomes richer if effect size estimates are taken into account. The analysis of Cohen's d values, indeed, has pointed out that the clearest and most sizeable between group differences concern short- and long-term memory (VMT subtest) and focused attention (FAT subtest), with large effect size estimates, followed by verbal (VFT subtest) and non-verbal fluency (NFT subtest) and inhibitory control (MGTA subtest), with medium-to-large effect size estimates. Subtests tapping on working memory (WMT) and efficiency of mechanisms for suppression of interference (MSTA), instead,

highlighted significant though less considerable effects, these being associated to small-to-medium effect size estimates.

To sum up, above-presented preliminary findings further stress the link between peculiar executive deficits and the substance-use disorder and provide first evidence in favour of the potential of the above-presented BFE-A as a quick yet valid neurocognitive screening tool, able to consistently highlight differences in higher-cognition and executive control efficiency between a cohort of patients diagnosed with substance-use disorder and a cohort of matched healthy subjects, as well as to outline a peculiar profile of stronger and weaker points in such high-level cognitive functions.

3.6 Structure of the BFE-A

3.6.1 Verbal Memory Test

Altered learning and memory processes are thought to lie at the core of dysfunctional motivational and reward mechanisms that, in addiction disorders, amplify the reinforcing value associated with specific behaviours or substances of abuse. Notably, the very same neural structures involved in those implicit dysfunctional learning mechanisms also underlie higher explicit mnestic functions. Such association is corroborated by a quite ample set of clinical studies, which consistently showed that processes mediating short-term maintenance and subsequent long-term storage of information are often impaired in people presenting addiction (Fernández-Serrano et al., 2011; Gould, 2010). Explicit, or declarative, memory involves conscious encoding and retrieval of information, facts and events from long-term memory after they went through short-term memory processing and maintenance, and is typically measured through recall or recognition tasks. Focusing on neurocognitive sequelae of addiction, in the majority of available studies, memory impairments were tested and quantified via learning and memory tests based on verbal material, such as word lists or short stories.

The Verbal Memory Test (VMT) of the BFE-A, then, aims at assessing short- and long-term memory through immediate and delayed recall trials. Specifically, it taps on encoding, consolidation, and retrieval processes for verbal material presented in auditory mode. The administration procedure is based on a list of 15 words, which is presented 5 times. After each presentation, the examinee is asked to verbally recall of the stimulus list. Then, after 10 min, the examiner asks the examinee to recall the list of stimuli again, with no additional cues.

The VMT was created starting from a conceptual and methodological revision of the most diffused neuropsychological tests for immediate and delayed recall of verbal items and, in particular, of the Rey Auditory Verbal Learning Test (Rey, 1958). Such classical neuropsychological test proved to be able to highlight memory deficit in a variety of neuropsychological clinical conditions (Andersson et al., 2006;

Bravin et al., 2000; Carlesimo et al., 1996; Schoenberg et al., 2006; Vakil et al., 2012). It was also used to assess memory deficits related to alcohol and substance abuse (Carbia et al., 2017; Fox et al., 2009; Hoffman et al., 2006; Jang et al., 2007; Solowij et al., 2011); though the analysis of literature highlighted a few critical issues concerning the item list included in the Italian version of the test and the general structure of the test. Specifically, the presence of latent semantic associations between the items of the word list may cause facilitation and favour intrinsic encoding strategies. Furthermore, the items in the list is constituted by both concrete and abstract words, which, however, have peculiar semantic features and a different representation in the conceptual linguistic system. Also, the length of the items presents significant variability. And again, preliminary clinical observations collected in a pilot study suggested that the test might be simple for some types of patients with addiction, especially in the younger ones.

Building on such preliminary observation and critical notes, during the development of the VMT we have created a new set of items, selected from the list of lemmas of the COLFIS corpus (Bertinetto et al., 2005) on the basis of stringent psycholinguistic properties: lexical class (nouns), category (concrete), number of letters (4–6), total relative frequency ($\geq$100). In addition, we opted for words that did not have direct latent associations (for example, sun-garden-window) or that did not belong to the same proximal semantic-conceptual network (for example, home-school). Moreover, in order to make the test more discriminative and sensitive even in the case of slight deficits in memory functions, in the VMT the examinee is asked to perform a serial recall task. Serial recall, indeed, compared to free and guided recall, requires a greater allocation of cognitive resources.

3.6.2 Working Memory Test

Deficits of working memory—being such function crucial for complex information-processing and, therefore, for any higher cognitive function—have been the object of extensive investigation in relation with both substance-related and behavioural addiction (Fernández-Serrano et al., 2011; Ioannidis et al., 2019; Yücel et al., 2007). Working memory is commonly defined as a limited capacity portion of the human memory system, where information is temporarily stored and kept accessible to consciousness so that is can be manipulated and processed in the service of higher cognition. As part of EF, working memory is often altered in people who developed addiction pictures and, in typical neuropsychological assessment procedures, is assessed via digit span or repetition tests.

The Working Memory Test (WMT) of the BFE-A aims, in particular, at assessing the working memory span for numerical material presented in auditory mode. Specifically, it taps on the mechanisms for storage and active processing of information in the short term. The administration procedure includes the presentation of numerical sequences of increasing length. After the presentation of each sequence,

the examinee is asked to repeat the series of numbers rearranged from the highest to the lowest.

The WMT was created starting from a conceptual and methodological revision of the most-diffused neuropsychological tests used to assess working memory defects and, in particular, the Digit Backward Test (Hebb, 1961; Wechsler, 1939). While the classic version of the backward digit paradigm appeared for the first time in the Wechsler Bellevue Intelligence Scale (Wechsler, 1939), several versions differing in materials, presentation methods, and scoring algorithms were developed in the following years. In its original version, the examiner verbally presents sequences of digits and then asks the examinee to repeat them in reverse order. Such test is commonly used during neuropsychological assessment of various clinical conditions in neurology, from head trauma, to stroke, neurodegenerative disorders, and others (Black, 1986; Laures-Gore et al., 2011; Luerding et al., 2008; Sartori & Edan, 2006). As a part of more extensive assessment batteries, it was also used for the evaluation of cognitive deficits in people presenting substance-related addiction (Cannizzaro et al., 2014; Copersino et al., 2009; Grohman & Fals-Stewart, 2004), especially from cannabis (e.g. Meier et al., 2012).

In order to overcome some critical issues concerning the structure of sequences that were pointed out during the critical analysis of the relevant literature, the WMT was equipped with new items, which was created using one-digit natural numbers, by controlling for the internal structure of the sequences and so to prevent the presence of ordered digit chunks and to avoid chunks constituted by contiguous even (or odd) numbers. Moreover, in order to increase the complexity and, therefore, the discriminating potential of the test, the WMT requires the examinee to mentally manipulate the information stored in the temporary buffers (i.e. before being produced, the sequence of numbers must be rearranged in descending order), thus increasing the cognitive workload and allowing to evaluate the efficiency of working memory during a challenging task.

3.6.3 Focused Attention Test

Among other executive deficits, the reduction of the ability to orient attention toward specific stimuli, to keep attention resources consistently on a continuous task, and maintain the focus while inhibiting distracters is commonly reported as a side-effect of substance use and addiction disorders (Fernández-Serrano et al., 2011; Gould, 2010). The ability to focus attention on a target task or stimulus for any period of time, thus making it possible to quickly and efficiently detect relevant information and plan appropriate responses is commonly referred to as focused attention. Such complex process, which is often inefficient in both acute substance administration and chronic drug abuse (Gould, 2010), plays a critical role in supporting higher cognition, together with working memory. Its impairment might thus worsen the efficiency of executive control and, therefore, of self-regulation skills of people who developed addiction.

The Focused Attention Test (FAT) of the BFE-A aims at investigating the ability to identify and parse out relevant stimuli while ignoring distracters during a challenging task. Specifically, it taps on the integrity of focused attention processes with visual-spatial material. The FAT is based on a decoding task involving graphics and numerical materials. The examinee is presented with a grid of graphic symbols and an encryption key displaying the association between numbers and symbols, and has to convert each symbol in the grid based on the encryption key within a limited time.

The FAT was created starting from a conceptual and methodological review of the most-diffused neuropsychological tests used to evaluate the efficiency of focused attention and, in particular, the Symbol Digit Modalities Test (Smith, 1973). Such test, inspired by Wechsler Digit Symbol test (Wechsler, 1939) was thought to tap on several components of attention, as well as information processing and working memory skills (Shum et al., 1990).

Performance at the Symbol Digit Modalities Test was found to be deficient in various categories of neurology patients (Owens et al., 2018; Reekes et al., 2020; van Walsem et al., 2018; Wu et al., 2020) and to be worsened in presence of concurrent anxiety or depression (Goretti et al., 2014; Joosub et al., 2017). Impaired performance at the test was also found in individuals who developed addiction to alcohol or substances, such as heroin, cocaine, amphetamines, MDMA, and cannabis (Cuyàs et al., 2011; Harvey et al., 2007; Jovanovski et al., 2005; O'Malley et al., 1992). Yet, the score of the original version of the test is known to be influenced by age, education, gender, and cultural factors (Kennepohl et al., 2004), as well as practice (Roar et al., 2016; Strauss et al., 2006).

During the design of the FAT, we performed an accurate revision of the graphic symbols used in the new version of the test and of its internal structure. Specifically, we have selected and validated new symbols and excluded graphical signs that could have recalled mathematical operators that, when coupled with numerical digits, could have evoked implicit facilitating associations. Furthermore, the encryption key has been rearranged in order to avoid that graphically similar signs were contiguous to each other, again to avoid any facilitation effect due to implicit learning of the sequence.

3.6.4 Verbal Fluency Test

Fluency is one of the main facets of the complex construct of cognitive flexibility, which can be described as the ability to direct and re-orient cognitive resources between different operations, stimuli, or responses, and to flexibly adapt mental processes, mindset, and behaviour in relation to different tasks, schemas, or changes in the environment. Fluency itself is commonly mirrored by the extent and variety of information retrieved from memory within restricted search parameters (e.g. the amount of unique words pertaining to specific semantic categories). To be efficient, it requires executive control over cognitive processes, such as selective attention and

inhibition, set shifting, and self-monitoring (Patterson, 2011). Cognitive flexibility proved to be affected by structural and functional alterations associated with addiction disorders (Antons et al., 2020; Brand et al., 2019; Fernández-Serrano et al., 2011; Koob & Volkow, 2016) and verbal fluency tasks are likely the most diffused methods for assessing such higher executive function in both neurology and psychiatric departments.

The Verbal Fluency Test (VFT) of the BFE-A aims at assessing the integrity of lexical access and selection mechanisms and the efficiency of self-monitoring and cognitive flexibility when dealing with verbal material. The administration procedure includes three 60-s trials. In each trial, the examinee is asked to produce as many words as possible that begin with a given letter (phonemic rule), excluding proper nouns and derived names with the same root.

The VFT was created starting from a conceptual and methodological revision of the most-diffused neuropsychological tests tapping on verbal fluency skills and, in particular, of the Controlled Verbal Fluency Task (Borkowski et al., 1967). Starting from the original version, numerous variants of the verbal fluency test have been developed based on different languages and letter sets (Kavé, 2005; Kosmidis et al., 2004; e.g. Novelli et al., 1986; Pena-Casanova et al., 2009; Raoux et al., 2010). Such tests proved to be valid and sensitive in identifying deficits of cognitive flexibility and impairment of verbal EF in the presence of frontal lesions or dysfunctions (Alvarez & Emory, 2006; Davidson et al., 2008; Henry & Crawford, 2004; Metternich et al., 2014), as well as neurodegenerative disorders, mild cognitive impairment, neurodevelopmental disorders, and depressive syndromes (Andreou & Trott, 2013; Libon et al., 2009; Obeso et al., 2012; Vaughan et al., 2018). Deficits of verbal fluency and cognitive flexibility have also been reported using phonemic fluency tests in individuals with alcohol and substance-related addiction (Kelley et al., 2005; McHale & Hunt, 2008; van Holst & Schilt, 2011). Yet, validation studies present a remarkable variability of core factors modulating examinees' performance (Ardila et al., 2000; Auriacombe et al., 2001; Loonstra et al., 2001).

Since the critical analysis of those evidence has mainly highlighted methodological shortcomings related to the stimulus letters, which were often chosen randomly, in designing the novel VFT, we have especially focused on the selection of such stimuli. In particular, in order to minimize potential biases caused by the originally random choice of the stimulus letters and to the consequent differences in the extension of the related vocabulary in different languages, in the present version of the phonemic verbal fluency test the stimulus letters have been selected following the following principles: presence of two consonants and one vowel; minimum number of lemmas starting with the stimulus letter in the reference vocabulary equal to 10.000 for the consonants or 25.000 for the vowel (based on the De Mauro's New Dictionary of the Italian Language); number of lemmas in the Italian vocabulary starting with the three newly selected stimulus letters equal to or greater than the number of lemmas associated with the original letters.

3.6.5 Non-verbal Fluency Test

While tests based on verbal fluency represent a sort of standard for the assessment of verbal EF in both neurology and psychiatry departments, non-verbal fluency tasks are remarkably less used in clinical practice, notwithstanding their clinical and diagnostic potential. Such tasks, indeed, allow to evaluate the integrity and efficiency of executive control on selective attention and inhibition, set shifting, and creativity not relying on verbal materials, thus overcoming potential biases or barriers due to cultural or linguistic differences.

The Non-verbal Fluency Test (NFT) of the BFE-A aims at testing the efficiency of cognitive flexibility mechanisms and the integrity of generative and creative processes based on visual-spatial patterns and graphical design. The test material consists of a series of 80 matrices constituted by 5 squared dots arranged according to a fixed schema (4 corners and a dot in the middle). According to the administration procedure, the examinee is asked to produce the greatest number of different graphic configurations by connecting, with straight lines, at least two of the five squared dots of the matrices, within a limited time.

The NFT was created starting from a conceptual and methodological revision of the few neuropsychological tests developed to evaluate cognitive flexibility and fluency via non-verbal material and, in particular, of the Five Point Test (Regard et al., 1982). Such neuropsychological test, which was initially created to offer a more structured and methodologically sound alternative to available visual-spatial fluency tests, had the merit to introduce different scores indicative of executive functioning, such as productivity, flexibility, use of strategic planning, as well as errors due to violations of the rules (Cattelani et al., 2011; Goebel et al., 2009). Several studies show that such test is sensitive to brain damage and, in particular, to structural and functional alterations of the frontal lobes (Goebel et al., 2013; Hansen et al., 2017; Lee et al., 1997; Tucha et al., 1999). Despite the clinical potential of the test and the relevance of cognitive flexibility deficits associated with addiction patterns, the use of non-verbal fluency tests for neurocognitive assessment of individuals with substance use disorder or behavioural addictions is poorly documented (Al-Zahrani & Elsayed, 2009).

The critical analysis of relevant literature, together with pilot testing of the BFE-A, resulted in a review of the test materials and in the updating of some scoring criteria. Namely, in the novel NFT, the matrices consist of a configuration of five squared dots, instead of round points, in order to optimize the figure-background contrast. In addition, the initial set of examples has been revised by adding a third configuration to clarify to the examinee that even the drawings formed by separate lines (for example, two parallel lines) are valid for the purposes of the test. Finally, in the NFT, the use of strategies in producing graphic configurations is of remarkable interest and is considered a peculiarly critical factor in evaluating the efficiency of high-order EF. For this reason, the defining criteria for identifying strategies in answers to the test have been expanded, including the use of rotation rules (serial reproduction of the same graphic configuration but rotated around its central point),

the use of enumeration rules (serial reproduction of similar graphic configurations, but created by addition or subtraction of traits), and the use of semantic-conceptual rules (for example, the sequential reproduction of the letters of the alphabet or of graphic patterns representing numerical digits).

3.6.6 Modified Stroop Task for Addiction

Further components of EF that proved to be critically impaired in people presenting substance-related or behavioural addiction are attention regulation and interference inhibition (Antons et al., 2020; Brand et al., 2019; Fernández-Serrano et al., 2011; Koob & Volkow, 2016). In particular, reduced executive control over endogenous vs. exogenous orienting of attention and inhibitory mechanisms aimed at lowering the subjective relevance of interfering stimuli might contribute to the severity of self-regulation deficits in addiction. And again, ineffective control over the distribution of the attention focus and available cognitive resources, especially when cognitive reserve is fading, may make it more difficult to refrain from automatic dysfunctional behaviours.

The Modified Stroop Task for Addiction (MSTA) of the BFE-A is a computerized neurocognitive task devised to investigate the integrity of those attention regulation processes and of mechanisms allowing for the control of interference due to semantic incongruence or salience of addiction-related stimuli. The task uses verbal material and quantifies the outcome in terms of accuracy, omitted responses, and response times. In the MSTA, the examinee has to respond to quickly-presented verbal stimuli by indicating the colour in which the stimulus words are written (four possible responses: red, green, blue, and yellow). The task includes both the classic contrast between congruent colour-word stimuli (e.g. the word "yellow" presented in yellow) and incongruent colour-word stimuli (e.g. the word "red" presented in blue), and a further contrast between neutral words (e.g. "canoe") and words associated with contexts and situations of substance abuse and dependence (e.g. "drunk"). Four alternative though comparable versions of the MSTA were created, focused on specific addiction pictures and different primary substances of abuse: stimulants, opioids/sedatives/hypnotics, alcohol, and cannabis/THC.

The MSTA was created starting from a conceptual and methodological revision of experimental procedures based on the Stroop effect and used as neuropsychological assessment tools for attention and emotional regulation deficits and executive control. The Stroop task was originally developed as a tool to quantify the processing speed of complex information and the cognitive cost of interference. Subsequently, a growing interest in the impact of emotion on cognition and inhibitory control mechanisms provided the background for the development of the Emotional Stroop Test (Williams et al., 1996), an adaptation of the traditional Stroop task for the measurement of interference caused by the emotional salience of a stimulus.

Specific versions of the emotional Stroop test have been used for the assessment of interference control deficits in psychiatric patients (Rao et al., 2010; Wingenfeld et al., 2011), and of attentional-emotional bias in people with alcohol addiction (Adams et al., 2012) or substance-related addiction, such as cocaine (Kennedy et al., 2014), heroin (Yang et al., 2015), and nicotine (Mogg & Bradley, 2002). Yet, studies aimed at validating specific Stroop tests for addiction are still scant (Cane et al., 2009; Cox et al., 2006; Gardini et al., 2009). Furthermore, the reliability of those versions of the Stroop task, while being higher than that of other tasks used to investigate addiction-related attentional bias (Ataya et al., 2012), has been questioned. The design and development of the four versions of the novel MSTA task were, then, guided by the critical analysis of relevant literature concerning the paper-pencil and computerized versions of the Stroop test and, in particular, of its versions dedicated to the investigation of the interference effect due to emotional salience of the stimuli.

3.6.7 Modified Go/No-Go Task for Addiction

A complementary aspect of previously-noted higher executive impairments in addiction is represented by the alteration of prefrontal inhibitory control mechanisms, which plays a crucial role in modulating motivational incentives to maintain goal-directed behaviour and flexibility of stimulus–response associations (Antons et al., 2020; Brand et al., 2019; Fernández-Serrano et al., 2011; Koob & Volkow, 2016). Such mechanisms allow to suppress prepotent responses and to minimize the influence of irrelevant actions, feelings, and thoughts, thus enabling behavioural accommodation to changing goals, contexts, and contingencies. Relevant for addiction disorders, it has been recently proposed that the efficacy of general inhibitory control moderate affective, cognitive, and behavioural responses to exogenous or endogenous triggers, as well as the drive toward engaging in specific addictive behaviours (Hahn et al., 2017). Inhibitory control manifests through response selection or response stopping, and such processes lie at the core of the most diffused tasks devised to investigate and quantify the ability to suppress prepotent—though useless, irrelevant, or dysfunctional—thoughts or behaviours, such as the stop-signal task and the go/no-go task.

The Modified Go/No-go Task for Addiction (MGTA) of the BFE-A is a computerized neurocognitive task specifically devised to assess executive control and response inhibition in addiction. The task investigates the attentional bias for salient stimuli associated with addiction-related contexts or experiences, quantifying its impact (as mirrored, for example, by an increase in false alarms or by a modulation of response times) on behavioural inhibition mechanisms. To quantify such impact, the task allows for collecting different behavioural performance measures, including accuracy, number of omissions, false alarms, and response times.

In the MGTA, the examinee is asked to respond as quickly as possible to a given stimulus (Go stimulus, for example the letter “M”) by pressing a button while

withholding his/her response when another stimulus (No-go stimulus, for example the letter "W") is presented on the screen. The associations between stimulus and response (or non-response) are defined at the beginning of the task. The task was devised to counterbalance such associations within the subjects to account for any perceptual bias. Specific to the MGTA, the task also involves the systematic manipulation of the background on which the Go and No-go stimuli are presented. The background can recall neutral semantic contexts (e.g. physical activity or environments/scenes of daily life) or be semantically associated with addiction-related contexts, tools, substances, or experiences. As for the MSTA, the MGTA includes four different though comparable sets of addiction-related backgrounds, associated with different primary substances of abuse: stimulants, opioids/sedatives/hypnotics, alcohol, and cannabis/THC.

The MGTA was created starting from a conceptual and methodological revision of the available literature on the use of the Go/No-go paradigm for the evaluation of cognitive control skills and of the efficiency of inhibitory mechanisms, which was primarily based on experimental evidence. Since its first definition, the Go/No-go task took the form of an experimental paradigm used to study attention and inhibitory control mechanisms and their neurophysiological correlates (Donders, 1969; Huster et al., 2013). Factors such as the relative frequency of Go and No-go stimuli, the duration of the trial, or the inter-stimulus interval affect the level of inhibitory control required by the task and, then, the interpretation of performance measures (Leblanc-Sirois et al., 2018; Wessel, 2018; Young et al., 2018). The Go/No-go paradigm was also used to investigate whether the pathological condition of addiction induces attentional bias in favour of the substance of abuse and inhibitory control deficits (Wiers et al., 2013). In particular, the majority of studies focused on higher cognitive processes and cognitive control skills in cohorts of individuals who developed addiction to alcohol (Campanella et al., 2017; Noël et al., 2007; Pennington et al., 2019; Petit et al., 2014), using words or images associated with alcohol consumption as stimuli or as contextual frames (Campanella et al., 2017; Pennington et al., 2019). More scant are the studies using the paradigm with reference to other drugs of abuse, such as nicotine and heroin (Liang et al., 2014; Scholten et al., 2019). In designing and implementing the MGTA, we capitalized on the critical analysis of relevant literature concerning the computerized versions of the Go/No-go task and, specifically, of its modified version for the evaluation of inhibitory control and attention bias induced by salient stimuli associated with the use of substances or addiction-related experiences.

3.7 Conclusions

The above-presented empirical evidence—together with previously reported models, data, and remarks concerning the extent and core features of executive deficits that systematically pair with substance-related and behavioural addiction disorders—suggest that the BFE-A might represent a valuable alternative to aspecific

cognitive screening tools that are actually used in clinical settings. Furthermore, taking into account the standards for cognitive assessment that are implemented by average drug assistance/treatment services, the novel battery provides an answer to the clinical need for informative and reliable neuropsychological assessment tools, as well as to the practical need for quick and usable measures.

Validation studies and data from normative samples support the diagnostic value of the battery, yet a few open questions and potential future developments have to be acknowledged. Firstly, conclusive remarks on the value of the BFE-A for clinical practice would benefit from further testing with different clinical cohorts, including representative samples of patients who developed behavioural addictions (e.g. pathological gambling, gaming disorder, problematic Internet or social-network use, compulsive buying, and others). In addition, the tool should be subjected to test-retest studies, so to better investigate the reliability of test outcomes over time. And again, future studies should focus on concurrent and divergent validity by testing the correlation between the battery outcomes and independent psychometric, behavioural, and cognitive measures, or by complementing current findings with paired neurofunctional data (e.g. EEG markers of information-processing, executive control, attention regulation, and cognitive effort; hemodynamic markers of functional neural activations or inefficient neural processing).

Furthermore, future investigations could also better explore the capability of the screening battery to discriminate between major executive deficits and subclinical dysfunctions, and test its sensitivity in detecting different degrees of cognitive impairment associated with different addiction pictures. Such goals might be pursued by devising and implementing additional subtests or complementary assessment tools to specifically explore, as an example, the integrity and efficiency of decision-making processes, which lie outside of the functions currently targeted by the BFE-A.

Again, by pushing forward the boundaries of assessment settings and by embracing a more ecological perspective on cognitive assessment, future versions of the screening battery might be completely converted into an easy-to-use (for example, totally digital) format that could be used even outside of care and assistance facilities (e.g. home-based testing) or might be improved to assess the efficiency of investigated functions in realistic and interactive contexts.

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Chapter 4
EFs in Pathological Gambling Disorder

Michela Balconi, Laura Angioletti, and Giulia Delfini

4.1 Introduction and Definition of Pathological Gambling Disorder

Gambling behaviour can be defined in different ways, such as "compulsive", "pathological", or "problematic" (Caretti & La Barbara, 2009). In the DSM-V (American Psychiatric Association, 2013) Gambling Disorder (GD) is placed in the "Substance-Related Disorders" section as "Non-Substance Related Disorder" and is referred to as "gambling disorder". It implies a significant compromise in family, work, and interpersonal life of the subjects. In order to be diagnosed, the person must present four or more of the following symptoms within a period of 1 year:

1. Needs to gamble with increasing amounts of money in order to achieve the desired excitement.
2. Is restless or irritable when attempting to cut down or stop gambling.
3. Has made repeated unsuccessful efforts to control, cut back, or stop gambling.
4. Is often preoccupied with gambling (e.g. having persistent thoughts of reliving past gambling experiences, handicapping, or planning the next venture, thinking of ways to get money with which to gamble).
5. Often gambles when feeling distressed (e.g. helpless, guilty, anxious, depressed).
6. After losing money gambling, often returns another day to get even ("chasing" one's losses).

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7. Lies to conceal the extent of involvement with gambling.
8. Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling.
9. Relies on others to provide money to relieve desperate financial situations caused by gambling

Over the years, several authors have developed assessment and screening tools for the diagnosis of GD. Many of them have been developed by examining the diagnostic criteria of DSM (*Diagnostic and Statistical Manual of Mental disorder, DSM*). For example, Winters et al. (2002) have developed the *Diagnostic Interview for Gambling Schedule*, a 20-question interview to investigate the age of onset of gambling, symptoms, course and impairments in family, and interpersonal life (Winters et al., 2002).

From the point of view of symptoms, the psychological and physiological symptoms that occur in people with GD are very similar to the symptoms that can be found in people with substance addiction. Indeed, individuals with GD show symptoms of: abstinence, such as restlessness and irritability, when they are not gambling; craving, or the impressible desire for gambling behaviour; tolerance, when they need to play more and more in order to reach the desired pleasant effect; inability to control impulses, since subjects declare that they experience strong instincts to play and they are not able to resist them; and pervasive and constant thought of the game, which obscures the concentration of the subjects (Marazziti et al., 2015).

An important element to take into account is the impairment of family, work, and interpersonal life caused by gambling. In fact, individuals with GD tend to spend a lot of time playing and concentrating all their energies in the game, with the consequence of neglecting, reducing, or even interrupting other activities of daily life, such as work, family, or social ones (Rosenberg & Feder, 2014). Furthermore, a recurring problem in the life of gamblers is economic instability. Indeed, they often have financial problems caused by gambling, such as debt or bankruptcy.

In addition, GD presents several comorbidities with other addictions and psychopathological profiles: it has often been associated with a substance-related disorder. In this sense, it is important to consider that the use of psychoactive substances influences development and course of GD, as these substances have negative consequences on decision-making and impulsivity. In addition, gambling was found to be associated with other personality disorders, mood disorders, in particular depression and anxiety (American Psychiatric Association, 2013; Erbas & Buchner, 2012).

Over the years, several authors have tried to differentiate the subjects, applying terminological distinctions such as “pathological”, “problematic”, “social”, or “at risk” players. In particular, Custer (1984) identified six types of players: professional players, for whom gambling is not an addiction but a real job; antisocial gamblers, who play illegally; casual social players, for whom gambling is merely occasional entertainment; constant social players, who make gambling their main entertainment or leisure activity, but do not let it interfere with their family or work life; neurotic players without addiction syndrome, who use the game to soothe boredom, anxiety, depression; and compulsive gamblers, who have no control over their

own behaviour, cannot manage their impulses and continue to gamble despite negative repercussions on their family, work, and interpersonal life.

According to Custer, in this last type of player, a mechanism is established that he describes as "model of the career of the player" (Custer & Milt, 1985). In fact, they would go through three stages: a first phase of winning, in which they experience intense feelings of pleasure following the winnings of money; a second phase of loss, in which they begin to lose and therefore experience negative emotions due to the loss itself, thus trying to compensate by playing further; finally, a third phase of despair, in which the situation becomes increasingly serious to the point of causing a strong feeling of despair as a result of the different repercussions of the game on family and work life.

Finally, it was observed that, in pathological gamblers, it is possible to find neurobiological and neuropsychological alterations similar to those found in individuals with substance use disorder (SUD). In fact, several neuroimaging studies have been conducted that confirm the similarity between SUD and behavioural addictions, specifically GD. For example, a reduction in the activity of the ventromedial prefrontal cortex (vMPFC) was observed in individuals with GD during certain tasks, such as Stroop test or during the presentation of signals associated with gambling (Potenza et al., 2003b). As we have seen, the vMPFC plays a key role in the decision-making circuit and in risk assessment (Potenza, 2006). In addition, as regards subjects with GD, they show impairments in the performance of the Iowa Gambling Task (IGT) as much as individuals with SUD (Bechara, 2003). The IGT is used to analyse the effect of reward sensitivity and to identify predictive indicators of GD. In particular, the factors that influence the choices of the individual in the decision-making process are analysed, distinguishing between high and low risk decisions (Balconi et al., 2015, 2014a), as we will explore in the next paragraphs.

4.2 How Are EFs Involved in Pathological Gambling Disorder?

Because Executive Functions (EFs, for a definition see Chap. 1) deficits frequently underlie addictive behaviours (Hester & Garavan, 2004), it is essential to study potential EFs dysfunction in GD. This is especially important because EFs deficits may have also implications for the capacity of individuals to benefit from psychosocial treatments for GD (Leblond et al., 2003).

As we underlined in the previous chapters, EF involves higher-level cognitive processes implicated in the formation of successful goal-directed behaviour (Lezak et al., 2004), including planning and initiating behaviours, anticipating (positive and negative) consequences of actions, and the ability to adjust behaviours based on environmental feedback.

Specifically, planning, judgment, decision-making, set shifting, anticipation, and reasoning are the cognitive processes required for the successful completion of any

complex behavioural or cognitive task. Also required in this context are the suppression of unnecessary input and output, and the inhibition of inappropriate responses.

As we have previously observed, EFs were first described as central executive by Baddeley and Hitch (1974) and have been characterized by Lezak as the dimension of human behaviour that deals with how behaviour is expressed (Lezak, 1982). Therefore, the definition of "executive functions" includes a large umbrella of multiple processes [such as decision-making, response inhibition, conflict monitoring, cognitive flexibility, and their possible relationship with reward-related decision-making processes (Moccia et al., 2017)] and several, different definitions of EFs exist, which refer to different cognitive and neuropsychological models. Accordingly, in studying EFs in GD, authors referred to different models and adopted different tasks to analyse this family of functions. The problems of the absence of a homogenous definition of EFs and the large variety of tools used to assess them in the clinical population has already been underlined in some meta-analyses (see Kerns et al., 2008).

In this regard, studies have identified cognitive deficits in GD across a variety of domains (van Holst et al., 2010). Specifically, response suppression is indexed by stop-signal and Go/No-Go tasks, which require subjects to withhold simple motor responses when a stop-signal occurs (stop-signal tasks) or when a particular kind of stimulus is presented (Go/No-Go tasks). The ability to suppress responses is dependent on distributed neural circuitry, including the right inferior frontal gyrus and bilateral anterior cingulate cortices (Aron et al., 2004; Hampshire et al., 2010). The majority of studies have reported impaired response inhibition performance (i.e. increased motor impulsivity) in GD.

Several studies indicate a general trend towards EF impairment in GD. Specifically, GD performance in various neuropsychological tasks compared to non-GD revealed impairment in planning (Goudriaan et al., 2006b; Ledgerwood et al., 2012), cognitive flexibility (Goudriaan et al., 2006b; Odlaug et al., 2011), and behavioural inhibition (Goudriaan et al., 2006b; Grant et al., 2012; Kalechstein et al., 2007; Odlaug et al., 2011; Potenza et al., 2003b; Roca et al., 2008). Other studies found deficits in episodic and working memory, as well as verbal fluency in GD (Leiserson & Pihl, 2007; Roca et al., 2008; Zhou et al., 2016). Finally, performance on IGT, which was designed to assess decision-making capacity under ambiguity and risk, is impaired in GD (see Goudriaan et al., 2006b; Brevers et al., 2012b; Ledgerwood et al., 2012).

Brain imaging data appear to be consistent with these findings, revealing aberrant patterns of hemodynamic responses in prefrontal cortices in GD (for a review, see Grant et al., 2016). Given that the lateral prefrontal cortices have a central role in the neural substrate of EFs and working memory (Wager & Smith, 2003; Zakzanis et al., 2005), taken together this evidence points to a dysexecutive cognitive basis for GD, possibly attributed to lateral prefrontal dysfunction (for a review, see van Holst et al., 2010).

GD may experience significant deficits in EFs compared with non-GD, meaning that GD may be associated with significant comorbid neurological dysfunction in

many individuals with gambling tendency. This is clinically significant when considering appropriate treatment strategies for this population, as EF difficulties may hinder an individual's ability to benefit from treatment for GD (Ledgerwood et al., 2012).

As outlined previously, problems with cognitive functions dependent on cortico-subcortical circuitry have long been implicated in the manifestation of GD. Behaviours in people with GD are often repetitive, hard to suppress, and are impulsive in that they result in negative long-term outcomes. Furthermore, people with the disorder often have difficulty shifting their thoughts and behaviour away from gambling towards other areas of life that may be less damaging. Therefore, the study of Hinson et al. (2003) is particularly interested in two cognitive domains often reported to be deficient in patients compared with controls in the extant literature: response inhibition and cognitive flexibility. In prior cognitive studies, there has been a lack of clarity regarding whether deficits stemmed from the pathophysiology of recurrent gambling itself or rather reflected deficits that can pre-date symptoms and exist in people "at risk". In this study, authors attempted to address this issue in part by recruiting a group of subjects with "at-risk" gambling, viewed as being in an intermediate state between health and disease.

A second main and relevant factor that could be implicated in EF deficit in GD is the impulsivity control and related impaired behaviour. Many studies have found correlations between GD and behavioural and self-report measures of impulsivity. Specifically, impulse control is thought to be associated with underlying deficits in function in particular areas of the brain (e.g. prefrontal cortex) that are related to EF (Hinson et al., 2003).

Indeed, GD has been associated with impulsivity and attention deficit: GD patients were found to perform significantly worse than control subjects on attention measures and showed more childhood behaviours related to attention deficits (Rugle & Melamed, 1993). More recently, neuropsychological measures of impulsivity, such as the reaction time and number of errors at Go/No-Go tasks, as well as the scores at the Barratt Impulsiveness Scale, were higher in GD patients than healthy control subjects, while highlighting the importance of this dimension in the clinical picture of GD (Fuentes et al., 2006).

4.2.1 Brain Correlates of EF in GD Deficits

As we have underlined before (see Chaps. 1 and 2) prefrontal cortex (PFC)-dependent neurocognitive functions have been of particular interest in addiction research (Goldstein & Volkow, 2011).

Although the function of the PFC is highly integrated, two partially distinct PFC networks have been implicated in different aspects of neurocognitive function. The anterior cingulate cortex (ACC), lateral inferior cortex, and dorsolateral prefrontal cortex (DLPFC) have been linked to so-called "cool" EF, including working memory, response inhibition, task switching, and conflict monitoring (Badre &

D'Esposito, 2009; Koechlin et al., 2003), and the ventral, medial, and orbitofrontal structures (VMPFC, OFC) manage the so called "hot" EF, more involved in reward/emotion-related functions, including valuation, emotion regulation, and decision-making (Bechara & Van Der Linden, 2005; Peters & Büchel, 2010).

Also, GD patients may share a common dysfunction at the level of the vMPFC. In line with this hypothesis, a recent study using a comprehensive neuropsychological battery measuring EFs, demonstrated that GD and alcohol-dependent patients showed a reduction of executive functioning performance on inhibition, time estimation, cognitive flexibility and planning tasks (Goudriaan et al., 2006a, b).

The first neuroimaging studies in GD indicate that abnormalities exist in the vMPFC and cortico-basal ganglionic-thalamic circuits (Potenza et al., 2003a, b). Neuroimaging studies have shown that EF tasks activate a variety of areas within the prefrontal cortex (Coull et al., 2004) and, in addition to this, activate areas with important connections to the PFC, such as the caudate nucleus, the putamen, thalamic areas (Monchi et al., 2001), cingulate and parietal cortex (Van Den Heuvel et al., 2003).

The deficits in EFs as found in GD and SUD groups are therefore likely to be associated with dysfunctions and clusters of abnormal activation of these brain structures and brain circuits (for a recent review, see Moccia et al., 2017).

More recently, abnormal activity of the right Middle Frontal Gyrus (MFG), consistent with previous research (De Ruiter et al., 2009; van Holst et al., 2012a, b; Potenza et al., 2003a, b; Tanabe et al., 2007), and increased activity of the left dorsal ACC has been observed in GD (Quaglieri et al., 2020). The neural reward system encompasses both subcortical and cortical areas (including frontal lobes) and through the release of dopamine can stimulate food consumption, social reproduction, but also neural responses for "unnatural rewards" (such as monetary rewards), that contribute to compulsive behaviours like for instance gambling (the same occurs for substances) (Comings & Blum, 2000). Indeed, the striatum has been frequently reported to be involved in the expectation of monetary rewards (Crockford et al., 2005; Miedl et al., 2012; Power et al., 2012; Reuter et al., 2005): individuals with GD displayed greater activation in the bilateral dorsal striatum, related to stronger associations between the action and its outcome (van Holst et al., 2010), which could be accounted for by an overestimation of the gambling outcomes. The hyperactivity of dorsal striatum regions appears to be linked to a higher degree of reward-seeking behaviour, which could be a compensatory mechanism correlated to reward gaps in GD (van Holst et al., 2010); whereas the ventral part of the striatum appears to be more involved in the processing of the rewards (Miedl et al., 2012).

Regarding the involvement of the frontal lobe, the fronto-striatal cortical circuit is crucial for EF (Robbins, 2007), encompassing reward processing, control, and motor planning (Meng et al., 2014). When the clinical syndromes of GD are more severe, a hyperactivation of the striatum leads to impaired ability to control gambling behaviour. This impairment may contribute to fronto-striatal dysfunction in GD, with individuals showing deficits in self-regulation and higher degree of reward-seeking behaviour. The loss of control over gambling conduct is therefore due to an imbalance of the dopaminergic system and the neural circuits connecting

subcortical structures, such as basal ganglia and limbic areas and frontal regions (Moccia et al., 2017).

4.2.2 *Empirical Studies About Behavioural Deficits in GD: Measurement Evidence*

A recent study showed that patients affected by GD undergoing a battery of neurological tests, namely, the Wisconsin Card Sorting Test (WCST), the WMS-R (Wechsler Memory Scale revised) and the FAS (Verbal Associative Fluency Test), had sufficient or normal intellectual, linguistic, and visual-spatial abilities. As far as the WCST is concerned, GD patients showed qualitative but not quantitative deficits: in fact, although no differences were found between GD patients and healthy control subjects in the total number of categories completed, different abnormalities were detected at some subscales. As compared with healthy subjects, the thinking of GD patients appeared perseverant, because when they tried to resolve a problem while using an incorrect method, they tended to continue beyond that point at which other subjects would have looked for alternative solutions. A similar behaviour has been observed in GD patients at both the card-choosing tests (Goudriaan et al., 2006a, b) and the Go/No-Go task (Fuentes et al., 2006).

The difficulty that GD patients showed in learning from their mistakes and in redirecting themselves in the appropriate direction represents one of the most characteristic features of patients with alterations of the prefrontal lobe. This aspect has been observed in a significant number of experimental paradigms, in particular, patients with lesions of the prefrontal lobe are sometimes able to identify correct answers, while nevertheless still continuing to produce wrong answers (Drewe, 1975; Lurija & Homskaya, 1964). These findings are also compatible with other studies reporting worse performances in cognitive "risk-taking" tasks in patients with prefrontal lesions, as compared with healthy control subjects or patients with temporal lobe excision (Miller, 1992). In addition, these data would suggest a more generalized frontal lobe impairment. This is also supported by a recent study showing behavioural evidence of an alteration of both DLPFC and orbitofrontal cortex (OFC) in GD (Brand et al., 2005). However, it is still unclear whether the observed frontal lobe abnormalities should be considered a primary phenomenon linked to the aetiology of GD, or secondary to some symptomatologic features, or to the comorbid psychopathological conditions.

Flexible responding has traditionally been assessed with the WCST and its variants, which are dependent on distributed neural circuitry, including the ventromedial and ventrolateral prefrontal cortices (Buckley et al., 2009; Hampshire & Owen, 2006). Consequently, the majority of available studies have reported on WCST performance in GD compared with healthy controls.

Goudriaan and colleagues (2006a, b) concluded that comprehensive EF deficits were present in the GD group compared to normal controls. The deficits found in

EFs in the GD group could not be explained by deficits in basic cognitive functions, which are proposed as a prerequisite for performance of EF tasks. Also, their results indicate that the GD group resembled the alcohol dependence group, suggesting that comorbid symptoms had limited influence on EF performance.

While regarding the impairment of decision-making observed in GD might be explained by the inability to inhibit irrelevant information: in a recent study, the performances on the reverse Stroop task, which highly discriminates the ability to inhibit interferences, were significantly impaired in GD patients than in healthy subjects (Kertzman et al., 2006). Moreover, neurocognitive indicators of decision-making and disinhibition, such as the Card Playing Task and Stop Signal Reaction Time, respectively, seem to be powerful predictors of relapse in GD (Goudriaan et al., 2008).

4.2.3 Behavioural Addiction, GD, and Substance Addiction: What Kind of Brain Correlates Relationship?

The current state of knowledge from neuroscience studies suggests that there may exist a common pathological pathway between SUD and non-substance-related disorder (e.g. gambling or Internet gaming disorder), involving dysfunctional reward mechanisms and deficit in cognitive decisional processes (for an in-depth description, see Chap. 1). Previous studies observed that the neurobiological patterns of the addictive behaviours are similar: for instance, there is a reduction in dopamine (DA) receptor on compulsive feeding (Wang et al., 2002) and gambling related to deficits of the frontal cortex in GD (Potenza, 2008).

Many of the features central to GD are similar to those of SUD and implicate common underlying dysregulation of frontostriatal circuitry (Clark, 2010; Grant et al., 2010). Notable features that share commonality between GD and addiction include persistent engagement in a behaviour despite negative consequences, loss of self-control, compulsive engagement (“drive”), craving, tolerance, and withdrawal (Potenza, 2008). As such, GD represents a valuable model for studying the neurobiology of addiction, without the potential confounding pernicious brain effects from chronic alcohol or illicit substance abuse.

Apart from the diagnostic similarities that GD shares with SUD and Impulse Control Disorders (ICDs), these disorders are all characterized by behavioural deficits in self-regulation, as manifested in an impaired ability to inhibit the urge for the desired behaviour or drug. Deficits in EFs are proposed as important mediators in drug bingeing (Goldstein & Volkow, 2002), and several studies suggest that impairments in EFs have a negative impact on treatment success and relapse in substance dependence (Bates et al., 2004; Fals-Stewart & Schafer, 1992).

4.2.4 Some Limits in EFs Studies Applied to GD

Despite the relevance of EFs in GD, research in this field is still scarce and findings are inconsistent. In addition, most studies did not investigate whether deficits in EFs were independent of deficits in basic cognitive functions. A closer look at the literature reveals a number of potential weaknesses in this notion. Firstly, there is evidence against a generalized EF impairment in GD (Manning et al., 2013). Secondly, several studies have a number of methodological limitations. The most important reason for these inconsistencies concerns the fact that some studies targeted only a single EF, most studies were restricted to small groups and studies often failed to assess and control for comorbid disorders and medication use. In addition, the specificity of EF deficits in GD is not known, because clinical comparison groups were not included in most of these studies. Sampling bias, mainly due to inclusion of treatment-seeking patients only, may provide non-representative groups (Lorains et al., 2011). Additionally, it has been argued that the majority of GD seek treatment for a co-morbid disorder rather than gambling per se (Winters & Kushner, 2003). Moreover, small sample size prevents the use of parametric statistics and limits generalizability of results. Finally, a large proportion of the relevant studies lack a thorough neuropsychological assessment, thus drawing conclusions on the basis of limited data.

The above limitations stress the need for further studies utilizing comprehensive cognitive batteries on representative, unbiased, ecological samples of individuals with GD.

4.3 Theoretical Models to Explain SUD and GD

Some recent neurocognitive models were introduced to explain drug dependence. However, they can be applied and extended also to GD, based on previous evidence on both behavioural deficits and neurocognitive correlates. We summarize some main directions of these models in the following paragraphs.

4.3.1 Aberrant Learning Theory

Chronic drug exposure leads to long-term associative memory processes occurring in several neural circuits that receive input from midbrain DA neurons (reward learning). Specifically, cues predict-rewards can strongly activate NAcc related circuitry in both animals and humans even better than the reward itself (Schultz, 1998). It was argued that explicit learning (declarative memory) could reinforce the addiction: usually people who take drugs since the first time learn, at conscious level, predictive relationships between some cues in the environment and rewards.

Abnormally strong explicit learning might distort declarative memories or expectations; such addicts make inaccurate predictions about the consequences of taking drugs. Even so, drugs cause strong implicit learning which is not directly accessible to conscious. *The Stimulus-Response (S-R) habit learning hypothesis* (Everitt & Robbins, 2005) proposed that the progression to addiction involves at first controlled behaviour by explicit and cognitive expectations about Act-Outcome relationships (memory of drug pleasure), and then occurs the automatic behaviour consisting of Stimulus-Response habits. Although habits are not intrinsically compulsive, the addiction is due to the development of very strong S-R habits. Considering the neural system of reinforcement for addiction, the changing from voluntary drug use to habitual and compulsive abuse represents a transition from PFC to striatal control, involving its dopaminergic innervation.

A similar explicative approach describing the transition from voluntary gambling behaviour to pathological and compulsive behaviour may be adopted for GD (Brevers & Noël, 2013). In this case, on the one hand, there are some structural factors of gambling games that could promote the repetition of gambling behaviour to the point that in some people it could lead to a dysfunction of controlling gambling conduct. On the other hand, there are three crucial neural systems whose dysfunction may lead to an impairment in controlling gambling conduct, and that will be described in the following paragraphs. Starting from the structural peculiarities of gambling behaviour, authors underlined that there are at least two properties of gambling that promote the repetition of playing behaviour: they are (a) the intermittent schedule for reward and loss, and (b) the illusion of control over the game (Brevers & Noël, 2013).

4.3.1.1 The Intermittent Schedule for Reward and Loss

Gambling is characterized by irregular wins and losses delivered on a variable ratio, which entails imperfect reward estimation. This may be one behavioural reason for why gamblers engage in gambling despite growing losses (Schultz, 2002). In fact, in previous studies, it has been demonstrated that behaviours learned after a primary learning phase featured by intermittent rewards are carried over time and far more resistant to extinction than conducts learned under continuous rewards (individuals stop the activity when it is no longer rewarded) (Schultz et al., 2003). Hogarth and Villeval (2010), for example, found that participants in the continuous-reward-schedule condition leave as soon as payment stops, while irregular monetary incentive schedules result in greater conduct persistence displayed by the participants at the end of the payment phase.

In line with the *Reward Prediction Error Models of Learning* (Montague et al., 1996; Schultz et al., 1993), a behaviour learned under intermittent reward learning requires imperfect reward prediction and it is much more resistant to extinction. According to the model, rewarding events that entail a better result than predicted (i.e. a positive reward prediction error) produce highly positive emotional activations, and these feelings remained stable if followed by a good prediction, and/or may

vary and be diminished by a reward that is worse than predicted (Schultz et al., 2003). Also, the release of dopamine co-varied according to the uncertainty of the reward, with higher amount of release for rewards with maximal uncertainty (Fiorillo et al., 2003). Therefore, when the roulette wheel spins and players win some money during gambling, they can experience a powerful emotional positive state, because the reward was so unpredictable or unforeseen.

4.3.1.2 Illusory Perceived Control

The second structural property of games supporting gambling behaviour consists of players option of arranging their own wagers (like picking a number at the lottery or selecting a colour at the roulette), which can boost players' belief that he/she could win (Ladouceur & Sévigny, 2005). The term adopted to describe this mechanism is "illusion of control", since none of the actions cited above have an effect on the probability of winning, and it has been described also in diagnostic manuals as a peculiarity of GD (American Psychiatric Association, 2013).

4.3.2 The Triadic Neurocognitive Model

As previously mentioned, a recent neurocognitive theoretical model includes gambling structural features in a more complete and exhaustive view (Brevers & Noël, 2013). Indeed, in addition to gambling games' characteristics, the model posits there are three crucial neural systems whose dysfunction may lead to an impairment in controlling gambling conduct:

- *A hyperactivation of an "impulsive" system* that is immediate, unaware, and unconscious and promotes automatic and repetitive actions.
- *A hypoactivation "reflective" system* that is slow and deliberative, predicting the potential implications of a behaviour, response inhibition, and metacognition.
- *The interoceptive system*, which transforms bottom-up bodily sensations into a subjective state of craving, accordingly, boosting the impulsive system, and/or weakening the normal functioning of the reflective system.

We distinctly consider these three neural systems and their implications in gambling behaviour.

4.3.2.1 The Hypersensitization Toward Gambling-Related Stimuli and the "Impulsive System"

Firstly, the authors try to answer to the following question: "how is it possible that individuals keep gambling despite growing monetary losses?" Authors advanced the hypothesis of a hypersensitization toward gambling-related stimuli and actions,

that is in line with the Incentive Sensitization Theory developed for SUD (Robinson & Berridge, 2003). Over time, gambling-related cue can activate disruptive motivational states, able to hinder high-order cognitive and affective systems adopted for controlling the behaviour and preventing the person from addiction-related conducts (Verdejo-Garcia & Bechara, 2009).

Through classical conditioning processes, the repeated gambling experience may promote the formation of associative learnings between gambling-related cues, the positive emotions derived from wins and gains, and the behavioural actions of gambling (Hofmann et al., 2009). These learned associations can be easily re-activated when the individual is confronted with gambling related cues, in the sense that his/her brain-body system is able to answer immediately to these attractive and salient stimuli, based on previous learning experiences, and may in a suitable way trigger the positive emotions and the behaviours linked to gambling (Hofmann et al., 2008, 2009). As for SUD, even gambling-related stimuli (considered as "unnatural rewards") may promote these quick and implicit activations (both at the memory and emotional level) and capture the attention of individuals with GD, leading to the so-called "attentional bias" (Robbins & Ehrman, 2004).

4.3.2.2 The Disruption of the Reflective Function

Although impulsive processes and hyperactivation toward gambling stimuli may explain individuals with addiction incentive to look for rewarding cues, it does not appear to explain the deficit in individual's capability to control the impulsive and immediate tendency to gamble, to implement a more functional and long-term goal-directed behaviour, a function that is mainly operated by the so called "reflexive system".

The integrity of the two following sets of neural systems is needed for the reflexive system to function: the "cool" and "hot" EF systems (previously described in Sect. 4.2.1). Also, successful decision-making represents the convergence of these two cognitive and affective processes, which results in the ability to optimally balance short-term benefits against long-term losses, or to predict the possible consequences of a given decision (Damasio et al., 1996). In contrast to the "impulsive" system, the functions of the reflexive system are managed through comparatively slow, monitored, conscious, aware, and self-regulated processes (Smith & DeCoster, 2000).

An impairment in "hot" EF could have an impact mainly in decision-making situations in which emotion regulation is involved, since there is no information related to reward probability (i.e. decision-making under ambiguity; Brand et al., 2006; Krain et al., 2006). In these conditions, previous associative memories of win or losses must be recalled foreseeing both short- and long-term positive or negative outcomes of any given option (Bechara, 2004) and an impairment of this ability in GD will be extensively described below.

Additionally, regarding the disruption in "cool" executive functioning, recent research on excessive gambling indicates that the capability to inhibit unconscious

immediate responses could be the critical element in the development and maintenance of gambling addiction. Indeed, impaired inhibitory control has been associated with the onset of addiction by exacerbating problem gambling (Brevers et al., 2012a) and sabotaging gambling withdrawal (Goudriaan et al., 2008).

4.3.2.3 The Role of Interoceptive Processes: Halfway Between Impulsive and Reflective Systems

As third system of the model, Brevers and Noël (2013) included the interoceptive system, as a halfway system that may play a role in the onset and maintenance of addiction by transforming bodily signals into feelings of desire, anticipation, or urge (Goldstein et al., 2009; Goldstein & Volkow, 2011). At the neural level, the area that mainly processes the interoceptive signals is the insular cortex (Craig, 2009). For further information on interoception and addiction, see also Chap. 9.

Furthermore, some recent theoretical discussions (Goldstein et al., 2009; Goldstein & Volkow, 2011) propose that the inability to grasp the interoceptive signals can affect the metacognitive capacity (i.e. the ability to reflect on one's own actions and thoughts, but also to assess one's own performance at the behavioural level, discriminating its success or failure (Cleeremans et al., 2007); for this concept, see also Chap. 1) in an individual with addictions. The deficiency of metacognitive capability in addicts has been well documented and it is extremely relevant for the clinical relapses, since the individual fails to understand the seriousness of the condition (Goldstein et al., 2009). The underestimation of addiction severity and a disconnection between self-perception and actual behaviour have been detected in different categories of substance users (cocaine, nicotine, methamphetamine, and cannabis users) (Chiu et al., 2008; Hester et al., 2009; Moeller et al., 2010; Payer et al., 2011); as well as GD (Brevers et al., 2013; Brevers & Noël, 2013).

4.3.3 Frontocortical Dysfunction Theory

A more neurocognitive model posits that the cortical impairment may strongly support the cognitive function impairment in both drug addiction and GD (Quaglieri et al., 2020). Chronic exposure to drugs can modify neural processing in frontal regions and distort functions of the PFC (Volkow et al., 2013). Dysfunctional changes in fronto-cortical activity have been described during intoxication for many of the drugs and in polysubstance abusers and a decrease of the volume of the PFC was also found in these populations (Volkow et al., 2013). Evidence show that fronto-striatal projections are important in regulating emotions and providing inhibitory control behaviour (Davidson et al., 2000). Furthermore, neurobiological studies report that some addicts show a variety of neuropsychological deficits shared with patients with frontal dysfunction (Bechara et al., 2000), such as deficit in decision-making (Verdejo-García & Pérez-García, 2008). It is widely accepted that PFC

is an important contributor to decision-making, assignment of value, and to maintenance of goal-directed behaviours (inhibitory control).

In our recent study, we focused on the metacognitive representation in Cocaine Addicts (CA) about the strategies they used during the IGT decision-making task (Balconi et al., 2014d). The IGT (Bechara et al., 1994) is a sensitive measure of decisional processing that simulates a real-world decision-making situation under uncertain conditions, and it implies some factors like: immediate rewards, delayed punishments, risk and uncertainty of outcomes. In the IGT, participants are instructed to try to gain as much money as possible by drawing selections from a choice of four decks; two of the decks are disadvantageous (DD), because they produce immediate large rewards and also significant money loss; the other two decks are advantageous (AD), because rewards and punishments produced are lower. In general, insensitivity to punishment, together with a strong reward dependence, results in a disadvantageous pattern of decision-making, and more reward-dependent individuals should make more risky and disadvantageous choice (Balconi et al., 2014b, d). Data showed different behavioural options and opposite strategies on the IGT comparing CA and healthy subjects: addicts demonstrated a more dysfunctional behaviour in their choice of strategy; moreover, they were unable to evaluate and reconstruct a realistic thinking about the cognitive strategy they adopted during the IGT performance (Balconi et al., 2014d).

It is widely accepted that the frontal lobes are involved in cognitive and metacognitive functions, and also the OFC and VMPFC, which are part of PFC, are networked with the amygdala, dorsal striatum, NAcc, hypothalamus, and insula. Thus, it has been hypothesized that addictive drugs produce a distorted and excessive DA signal in the OFC and other regions of the PFC, and this excessive DA signal can produce overlearning of drug-related cues. In general, impairments in executive function and increased impulsivity have been correlated with the diminished ability to recruit high cognitive functions of the PFC in drug abusers. Thus, pathological over-evaluation of drug related cues and impairment of some functions of top-down control could make significant deficits, such as loss of control and absence of coherent meta-representation about their own strategy in decisional making processes in addiction.

4.3.4 The Cortical Unbalance Model and Lateralization Effect

Previous neuroscientific literature demonstrated an association between addiction and the abnormal functioning of neural systems supporting motivation and reward processing.

As previously underlined in Chap. 1, the development of a problematic addiction disease (related or non-related to substances) has been mainly linked to deficit in reward pathways, neurocognitive deficits, attribution of value to salient stimuli (Balconi et al., 2014b, d; Bechara, 2005; Goldstein & Volkow, 2002), neural changes in memory structures (Volkow et al., 2003), and impaired metacognitive processes (Balconi et al., 2014b, d; Goldstein et al., 2009). Regarding SUD, previous works

indicated that addiction to substance is linked to the salient properties of drugs, which are strictly connected to a rewarding effect (Balconi et al., 2014b, d).

One of the main characteristics of SUD and behavioural addiction is the dysfunctional preference for instant gratification (i.e. reward) rather than a delayed gratification, which is observable in behaviours characterized by impulsivity. Several fMRI studies supported this dysfunctional process displaying higher amygdala activation to addiction-related cues (Volkow et al., 2013). For this reason, individuals with addiction have been compared to patients with VMPFC damage, highlighting how both clinical categories are characterized by insensitivity to future consequences (Bechara, 2005): in fact, as previously mentioned, they display the so-called "myopia for the future", being mainly compelled in obtaining a short-term gain, and unconscious of long-term beneficial or adverse outcomes (Balconi et al., 2014a, b). This aspect has been extensively studied by adopting decision-making tasks, such as the IGT. Interestingly, the repetitive use of substances and problematic gambling could also induce individuals not previously displaying deficit in decision-making, to develop an impairment in evaluating the long-term adverse consequences of their actions and prefer short-term rewards for having relief from the negative mood.

4.4 Behavioural Study and EFs in GD

As mentioned in several points in the chapter, the IGT is one of the most used behavioural tasks for assessing decision-making deficits in multiple categories of patients, from patients with frontal lesions to SUD individuals, to patients with GD. Previous studies demonstrated that GD-impaired performance at the IGT task is comparable to that of individuals with SUD (Goudriaan et al., 2006b).

A more recent work sought to classify decision-making deficits in GDs and investigate distinct features in two types of decision-making; under uncertainty and under risk, with two different versions of the IGT (Ochoa et al., 2013). As key findings, the authors indicated that the majority of GDs had general decision-making deficiencies, which were characterized by myopia for the future rather than aversion to punishment. Also, GDs mainly showed abnormal choice behaviour in relation to decisions made under risk on the IGT (linked to the explicit understanding of the task, EF, control processes, and impulsiveness) more than decision-making under ambiguity. It is worth noting that the authors highlighted that different pattern of deficits are involved in GD decision-making processes, and the predictors vary depending on the reinforcement schedule (Ochoa et al., 2013).

Moreover, basic research studies on the IGT demonstrated that decision-making under ambiguity features the first phases (trials) of the task, when the understanding of the rules is less explicit to the subjects (and the game depends primarily on emotional feedback processing), while decision-making under risk characterizes the final phases of the task, when the rules become more explicit (and the game relates with other complex mechanisms of EFs, such as categorization, task monitoring, and cognitive flexibility) (Brand et al., 2007).

Therefore, despite Bechara (2001) claiming that to obtain a good performance on this task, individuals should listen to and follow their feelings and intuitions (in line with *Somatic Marker Hypothesis*), we agree with previous studies stating somatic signals are essential for decision-making processes, but the integrity of the cognitive processes also depends on EFs (Brand et al., 2007).

Overall, findings described above suggest the need for specific clinical approaches based on learning techniques to support people to deal with decreased inhibitory control and impaired decision-making ability (Goudriaan et al., 2008). For treating GDs effectively, it has been also suggested that interventions should include methods for identifying the impulsive reaction before acting, in order to support them in reflecting on the long-term consequences of their actions, to control their behaviour, and to find possible alternative solutions (Álvarez-Moya et al., 2011).

4.4.1 Reward Sensitivity and IGT

Theory and past research using monetary incentive tasks, such as IGT, suggest that individuals' sensitivity to reward and loss plays a role in their ability to anticipate positive versus negative consequences that may result from their actions (Bjork et al., 2004).

As we know, and we already described in Chap. 1 (Sect. 1.6.2 on reward mechanisms in behavioural addiction) in the IGT, participants choose from four decks of cards across 50 trials, with the goal of acquiring as much money as possible. Decks vary in both the magnitude and frequency of rewards and losses. As such, the task can be used both to assess sensitivity to reward as well as sensitivity to loss. Importantly, the IGT is sufficiently complex that participants are unable to calculate the net gains and losses that each deck affords (Damasio et al., 1996). Rather, according to the hypothesis of somatic markers, participants must rely on covertly and overtly occurring marker signals to sense which decks are good, and which are bad, with correspondingly better versus worse likely future outcomes. For example, one study found that healthy subjects exhibited a Skin Conductance Response (SCR) prior to selecting a card from a bad deck, whereas patients with ventromedial frontal damage, who typically perform poorly on the task, did not (Bechara et al., 1996). Poor performance on the task is hypothesized to indicate individuals' less effective cue detection of these marker signals regarding possible future outcomes, which in turn may affect real-time decision-making.

Healthy participants will learn which decks are advantageous and will select more often from these decks, while patients with VMPFC lesions will persist in selecting from the DD that provide a large immediate reward (Bechara et al., 1996, 1997). More interestingly, healthy comparisons showed anticipatory SCRs when they choose decks, and the SCRs were higher when choosing disadvantageous decks; however, the VMPFC patients did not show the same anticipatory SCRs (Bechara et al., 1996, 1997).

Based on the studies in VMPFC patients (e.g. Damasio et al., 1991; Damasio, 1994), Damasio proposed the famous Somatic Marker Hypothesis: he argued that these patients had decision-making deficits because they were not able to use somatic markers to guide their decision-making. The somatic markers are body-generated, emotion-based signals (see also Dunn et al., 2006).

However, there are several limitations of the SCR studies. First, in the psychophysiology analysis, the deck that participants selected at last was used to designate each anticipatory "somatic marker"; however, in the deck selection phase, participants were free to shift their attention across all decks prior to selecting one. This procedure meant that the anticipatory SCRs may not reflect attention to a single card but shifting attention across all decks before making a choice (Dunn et al., 2006). Second, a study using the IGT in rhesus monkeys showed that SCRs were associated with the anticipation of a reward after a decision had been made rather than reflecting the decision-making process directly (Amiez et al., 2003). Thus, due to the low temporal resolution of SCRs, it was difficult to separate the signal related to response selection from the anticipation of feedback after the response (Dunn et al., 2006). One solution is to use other psychophysiological responses with a faster time course, such as Event-Related Potentials (ERPs).

4.5 Electrophysiology of Pathological Gambling behaviour

4.5.1 ERP Evidence for GD

To examine the electrophysiological correlates of GD, some research has explored widely-known ERPs, which have been documented to mark brain activity variations associated with selective attention and inhibition (for a review see, Luijten et al., 2014).

Some specific deflections were studied, mediating different cognitive processes. Two main ERP components have been reported to reflect changes in brain activity related to inhibitory control (Kok et al., 2004). Specifically, accumulating evidence suggests that the N2 and P3 reflect functionally distinct processes associated with inhibitory control. Accordingly, less pronounced N2 or P3 amplitudes in addicted populations relative to controls can be considered markers for neural deficits in inhibitory control.

4.5.1.1 N200

The first component, the N200 (or N2), is a negative-going wave emerging 200–300 ms after stimulus presentation. The neural generators of the N2 appear in the ACC (Huster et al., 2010; Nieuwenhuis & Yeung, 2003) and the right inferior frontal gyrus (IFG) (Lavric et al., 2004). The N2 is believed to index a top–down mechanism needed to inhibit the automatic tendency to respond (Falkenstein, 2006;

Kaiser et al., 2006) and corresponds to behavioural outcomes of inhibitory control (Dimoska et al., 2006; Falkenstein et al., 1999; Van Boxtel et al., 2001). The N2 has further been associated with conflict detection during early stages of the inhibition process (Falkenstein, 2006; Nieuwenhuis & Yeung, 2003). Consequently, the N2 can be interpreted as an index for early cognitive processes necessary to implement inhibitory control rather than the actual inhibitory brake.

ERP findings in behavioural addicted individuals (excessive Internet users) showed reduced N2 amplitudes, suggesting a deficit in the conflict detection stage of the inhibition process. In contrast, N2 amplitudes in people with excessive gaming behaviour were enhanced in a parietal cluster (Luijten et al., 2014).

To go into more detail, various and different N2 subcomponents have been reported according to the generation sites, the experimental tasks, and the underlying cognitive process (Patel & Azzam, 2005): the N2a is mainly generated in frontal sites by conscious attention to an oddball stimulus; the N2b is mainly evoked in central sites and is related to conscious stimulus attention; the N2c arises in frontal and central regions, in relation to classification tasks; finally, the N2pc, with a posterior distribution, is evoked during visual perceptual tasks involving the discrimination of a featured target showed in a field with distractors, it is an indicator of attentional selectivity (Treisman & Sato, 1990).

4.5.1.2 P300

The P3, the second ERP component involved in inhibitory control, is a positive-going wave emerging 300–500 ms after stimulus onset. The source of the P3 has been found to be close to motor and premotor cortices (Ramautar et al., 2006). Hence, P3 amplitudes appear to reflect a later stage of the inhibitory process closely related to the actual inhibition of the motor system in the premotor cortex (Band & Van Boxtel, 1999).

Some studies show that the reduced amplitude of P3 may be an indicator of the neurobiological vulnerability underlying disorders such as addictions (Patrick et al., 2006). In this regard, a recent study found a neural index underlying the response inhibition difference between individuals with Internet Addiction Disorder (IAD) and a control group by using an ERP technique (Dong et al., 2010). As discussed above, N2 is believed to be related to the process of conflict monitoring, and P3 to response evaluation: these two mental processes are fundamental abilities in the impulse inhibition process, and these two ERPs are frequently examined together in electrophysiological studies. Internet-addicted participants were expected to show some difference in N2 and P3 compared with their normal peers. Indeed, significant difference was found between IAD and normal groups in No-Go condition, the IAD group elicited significant lower N2 mean amplitude than normal group. The difference was largest at the central sites, as compared with frontal sites and parietal sites. In addition, the peak latencies in No-Go conditions were significantly longer than Go conditions in both IAD group and normal group.

Further analysis between groups showed that IAD group showed significantly higher P3 amplitude than normal group in No-Go items. In peak latencies of P3, IAD group elicited significantly longer P3 latency than normal group in No-Go condition, but no significant difference was found in Go condition. Thus, the size of P3 amplitudes in the present experiment might reflect the degree of cognitive endeavours when the participants successfully inhibited their impulse to respond. The IAD group elicited higher P3 amplitude than the normal group, and this evidence was interpreted as the need for more cognitive endeavours for behavioural addicted participants to successfully inhibit their response impulses. The NoGo-P3 latency was longer in IAD-afflicted participants compared with that of normal subjects. Peak latency is associated with cognitive efficiency. P3 latency is an indicator of processing speed suggesting that IAD had less efficient information processing function than their normal peers (McEvoy et al., 2001; Polich & Criado, 2006). On the other hand, the longer P3 amplitude may be related to impaired impulse control: evidence from studies on impaired inhibitory ability shows that individuals with Post Traumatic Stress Disorder and Parkinson's disease have longer NoGo-P3 latency compared with control groups (Bokura et al., 2005; Shucard et al., 2008). In summary, IAD participants displayed less efficient brain function not only with respect to information processing, but also response inhibition. Taking all features of N2 and P3 components into consideration, we can comprehensively understand impulse control in the IAD individuals.

In other studies, reduced P3 amplitudes to rewarding stimuli have been found for frequent gamblers compared to non-gamblers (Oberg et al., 2011), and in individuals with SUD (Goldstein et al., 2008). It is also of value to confirm whether problem gamblers abnormally process the significance of positive outcomes. A recent study revealed that the P3b subcomponent is likely to be driving the observed valence differences in global P3 amplitude (Lole et al., 2013). From this point on, references to the P3 will relate to the traditionally conceptualized global P3 component that comprises various subcomponents, including the P3a/novelty P3, P3b, and Slow wave, and it will be identified by its topography, latency, and experimental determinants.

4.5.1.3 ERN and FRN

The examination of the feedback-related negativity (FRN) ERP component was also considered a relevant effect in GD. Similar to the error-related negativity (ERN) that is elicited by commission errors in reaction time tasks (Falkenstein et al., 1999; Gehring & Willoughby, 2002; Miltner et al., 1997), the FRN provides insight into how feedback on reward and non-reward/punishment outcomes are evaluated in the brain. This component has been consistently shown to be sensitive to valence and context manipulations. Specifically, larger FRN magnitudes are observed when feedback signals monetary loss compared to gain (San Martín et al., 2010; Toyomaki & Murohashi, 2005; Yeung et al., 2005) or the least desired outcome within a particular context (Holroyd et al., 2004) during tasks that resemble gambling

activity. The reinforcement learning theory (Holroyd & Coles, 2002) postulates that the ERN and FRN reflect the activity of a high-level error-processing system within the mesolimbic–dopaminergic pathway, a system believed to be involved in the evaluation of environmental stimuli, the activation of motivated behaviours, and association formation.

Little and colleagues' (2012) study showed increased error rates for No-Go trials in people with excessive gaming behaviour compared with controls (Littel et al., 2012). Lower ERN amplitudes were found in participants with excessive gaming for error trials, suggesting that initial error processing in excessive gamers may be less pronounced than in controls, whereas error awareness may not be related to increased error rates.

Our recent research explored the main factors able to influence the subjects' choices in the case of decisions and distinguish between high- and low-risk decisions. Behavioural responses at the IGT, meta-cognitive strategy, and two ERP (FRN and P3) effects were used as predictive markers of gambling behaviour. Behavioural activation system (BAS) reward measure was applied to distinguish between participants with high-BAS and low-BAS levels. It was found that higher-BAS participants opted in favour of the immediate reward, with a concomitant dysfunctional metacognition of their strategy: a consistent "reward bias" affected the high-BAS performance reducing the P3 and FRN in response to unexpected (loss) events.

Regarding the EFs and metacognition, it was shown that impaired working memory can lead to poor decision-making capacity, with a consequential inability to plan the best long-term strategy, to inhibit the immediate reward-seeking, and to organize a functional behavioural response (Bechara & Martin, 2004; Verdejo-Garcia & Bechara, 2009). In particular, these functions under uncertain conditions, flexibility, and adaptation in behaviour were required to preserve the processing of consequences of previous decisions and actions (Perry et al., 2011). Recently, some research contributed to clarify the role of cognition and metacognition in gambling behaviour, and some specific ERP effects, such as the FRN and P3 effect, were considered the neurocognitive correlates of decisional behaviour in case of both functional and dysfunctional conditions.

The first ERP effect related to FRN is involved in performance monitoring, and it was observed that it is probably cortically generated near the MFC, mainly the ACC (Hewig et al., 2007). In addition, processing underlying the FRN are triggered by phasic dopaminergic signals, which code reward prediction error. These prediction error signals may then be conveyed to the ACC where they lead to adjustments in subsequent action selection and FRN production as an ERP effect (Holroyd & Coles, 2002).

A second relevant ERP deflection, the P3, was used to explore the impairment of the EFs in decisional processes (i.e. the difficulty in updating the incoming contextual information.) The P3 is the ERP component commonly investigated during feedback processing; it has been shown to be sensitive to the significance and occurrence probability of a stimulus (Hajcak et al., 2005; Oberg et al., 2011) as well as task complexity (Duncan-Johnson & Donchin, 1977). The increasing amplitude

of this positive deflection might represent the necessity to restore adjunctive information to updating the context (Balconi & Crivelli, 2010; Isreal et al., 1980; Johnson & Donchin, 1980) when an unattended event is observed. Thus, it was found that more unexpected outcomes (as in case of losses) generated an increased P3 in comparison with more expected (gains) outcomes.

Therefore, when considered together, these two ERP measures could signal the increased inability to adopt an adequate cognitive strategy in response to a decisional context.

4.5.2 EEG and Lateralization Effect

In line with the reward and lateralization model (for this concept, see also Chap. 1, Sect. 1.6.3 on the cortical unbalance model), we propose that a similar cortical left "unbalance" could be suggested in GD as for SUD.

Previous research works based on Gray's BIS/BAS model (Gable et al., 2000), indicated that behavioural motivational responses related to personality characteristics are essential for two main aspects: for generating emotions, and approach (reward) and withdrawal (inhibition) behaviours in the decisional process (Gray, 1981; Yu & Dayan, 2005). With respect to reward mechanisms, the BIS/BAS scale is a valuable instrument for evaluating possible anomalous reward sensitivity in neuropsychiatric populations, such as addictions, relative to healthy subjects (Gray, 1981; Gray & Naughton, 1987; Yu & Dayan, 2005). It permits to quantify the prevalence of BIS or BAS in individuals. As we have seen, the BAS motivational component has been conceived as a mechanism sensitive to compensation, incentive stimuli, reward, and non-punishment, involving actions directed towards a gain and away from a loss (Gray & Naughton, 1987).

Therefore, approach behaviour is promoted by reward, which induces a positive reinforcement for action, whereas avoidance behaviour (withdrawal) is reinforced by punishment. A normal level of BAS has a functional influence on positive emotional attitudes, while severe BAS and reward sensitivity levels have been related with impulsivity disorders (Fowles, 2000), and high levels of BIS have been associated with anxiety disorders (Balconi et al., 2014c; Balconi & Mazza, 2009; Yu & Dayan, 2005).

A crucial aspect of the BIS/BAS system (as previously explained in Chap. 1) is its cortical correlation with the PFC structures: while the left PFC activity was shown to be involved in approach-related motivations (appetitive) and positive emotions (reward processing), it was found that the right PFC activity was involved in withdrawal-related motivations (aversive) and negative emotions (punishment) (Gray, 1987; Quay, 1998).

Former studies showed that individuals with SUD, GD, or high-level of BAS reward sensitivity exhibited substantially more risky decision-making, preferring a greater possible reward even at a higher penalty risk. In addition, in these populations, their electroencephalographic behaviour showed a left PFC (DLPFC and ACC)

frontal hemispheric activation asymmetry found at the electrophysiological level, suggesting an enhanced sensitivity to more risky choices (Gray, 1981; Yu & Dayan, 2005).

A recent line of research investigated gambling tendency in a group of individuals with high-BAS scores and found that, in comparison with low-BAS, the high-BAS group showed an increased tendency to opt in favour of the immediate reward (losing strategy) instead of the long-term option (winning strategy), and members of this group were more impaired in metacognitive monitoring of their strategies and showed an increased left hemisphere activation when they responded to losing choices. A "reward bias" effect was hypothesized to act for high BAS, based on a left hemisphere hyperactivation (Balconi et al., 2015, 2014c; Finocchiaro & Balconi, 2015, 2017).

An earlier EEG study by Goldstein and Carlton (1988) studied lateralization of EEG activity in eight pathological gamblers and eight normal controls, matched for age and socio-economic status. The authors hypothesized that GD is associated with compulsiveness, and therefore expected difficulty switching between behaviours in GD. Therefore, they investigated switching between hemispheric activities, by employing tasks that typically involve left or right hemispheric activity. In the GD group, no significant shifts in right or left hemispheric activation existed, while in normal controls, these shifts were present. Furthermore, it took the GD group significantly longer to activate either left or right hemisphere. This last finding could have influenced the lack of lateralization differences, since less data with lateralized activation in the GD group was available. A possible explanation of the results is that the ability to shift brain activation on task demands is decreased in GD. This implies that an inflexibility in brain activity could lie at the base of GD, leading to perseveration and persistence in gambling activities, despite the negative consequences.

While an imbalance between prefrontal structures and the mesolimbic reward system has been related to addictive behaviour, whether their dysfunction in GD is reflected in the interaction between them and their lateralization remains unclear. Koehler and colleagues (2015) strive to address this question using functional connectivity resting-state fMRI in individuals with GD and controls. GD patients demonstrated increased connectivity from the right middle frontal gyrus to the right striatum as compared to controls, which was also positively correlated with non-planning aspect of impulsiveness, smoking and craving scores in the GD group. Moreover, GD patients demonstrated decreased connectivity from the right middle frontal gyrus to other prefrontal areas as compared to controls. The right ventral striatum demonstrated increased connectivity to the right superior and middle frontal gyrus and left cerebellum in GD patients as compared to controls.

The seed regions used by this study for the functional connectivity analysis were lateralized to the right hemisphere because of a previous voxel-based morphometry study (Koehler et al., 2015) showing a significant difference in local grey matter volume centred in right PFC and right striatum between GD patients versus matched controls. The right lateralization is consistent with previous evidence showing that the prefrontal EFs, such as inhibitory control, are mainly situated in the right

hemisphere (Aron et al., 2004; Simmonds et al., 2008). Moreover, the involvement of right PFC has also been shown for self-regulation (Cohen & Lieberman, 2010; Knoch & Fehr, 2007). With respect to the reward system, imaging studies on GD reported right lateralized changes during reward processing: alterations only in right ventral striatum have been found in response to gambling stimuli (van Holst et al., 2012a) as well as during the processing of monetary reward (Reuter et al., 2005). However, this study is not without limitations since it involved mainly male subjects and considered specific targeted seed regions.

Given these premises, it is possible to state that further clinical EEG studies are needed to determine the presence and direction of the cortical imbalance in groups of GD patients.

4.6 To Summarize: Gambling Between Specificity and Uniqueness

The present chapter highlights the actual solely behavioural addiction included in the DSM-V under the non-substance related disorder, which is GD. What mainly distinguish GD from SUD is the absence of substance intake that is replaced by a repetitive and pathological behaviour. Indeed, in GD, there are no physical signs of pharmacological withdrawal, as frequently reported in SUD; however, irritability, anxiety, and sadness can be described when the gambling activity is interrupted voluntarily.

Before, several behavioural and neural parallels were previously traced between GD and SUD, and those include neural responsiveness in specific brain areas (such as frontocortical circuits and reward system structures), loss of control over the behaviour, tolerance aspects, withdrawal, repeated ineffective attempts to avoid or stop playing, and impairment of normal functioning (American Psychiatric Association, 2013).

Regarding the cognitive functioning, it is interestingly noticed that these disorders share the progressive loss of control in terms of amount of time dedicated to obtaining the substance or to be engaged in the repetitive behaviour. Progressively, all individual's activities revolve around the gambling behaviour, and he/she displays impaired cognitive control in cutting down or regulating the gambling activities. Reduced levels of self-control, indicating possible deficit in the inhibitory control brain networks, and higher degree of reward-seeking behaviour were found to characterize GD. Interestingly, the so-called "myopia for the future", the lack of metacognition and the possible impairment in interoceptive processes has been described in GD by discussing theories and models, behavioural study, and electrophysiological research.

To conclude, despite the relevance of EFs in GD, research in this field is still scarce and findings are not always consistent. Study limitations stress the need for further research utilizing comprehensive cognitive batteries, but also neuroscientific

methods (such as EEG and specific ERP analysis) on representative, unbiased, ecological samples of individuals with GD. Within this framework, we strongly believe the study of EF deficits deserve further attention and are extremely important in GD, because EFs integrity may have implications for the capacity of individuals with GD to seek a cure, to benefit from psychosocial treatments, and to avoid relapses.

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Part II
Prevention and Treatment of Addictions

Chapter 5
Neuroenhancement of the Executive Functions in Addiction

Michela Balconi and Laura Angioletti

5.1 Introductive Remarks

As shown in the previous chapters of this book (Chaps. 1 and 4), neuroscientific theories of addiction highlighted how in individuals with dependence two major complementary systems are compromised: the impulsive or salience system, which becomes sensitized to drug stimuli and drug-related behaviours, and shows weakened reactivity to alternative reinforcers; and the reflective or executive system, which has limited capacity to inhibit impulsive responses and predict the behavioural consequences of an action (Bechara, 2005; Goldstein & Volkow, 2002, 2011; Verdejo-Garcia & Bechara, 2009).

Cognitive and neuroimaging findings typically endorsed the neuroscientific models of addiction, since substance users, regardless of the substance of use, exhibit drug-related attentional biases, poor emotional regulation and impaired executive functions (EFs) [i.e., working memory (WM), cognitive control and decision-making (DM)] (Fernández-Serrano et al., 2011; Littel et al., 2012). Some of these impairments could be pre-existing since impulsivity and frontal-striatal alterations have been observed in the siblings of alcohol users and individuals at high risk of developing substance use disorders (SUD) (Ersche et al., 2012; Verdejo-García et al., 2008); nonetheless, there is now significant evidence that chronic substance use can cause or intensify cognitive deficits in the two systems mentioned

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previously (Belin et al., 2008; Contreras-Rodríguez et al., 2015; Verdejo-Garcia et al., 2015).

Modern cognitive training interventions can rehabilitate and improve some of these deficits, but so far, the precise underlying mechanisms of these training, as well as their ability to transfer the acquired skills into real-life conditions, are still being discussed (Au et al., 2015, 2016). As a result, while there is theoretical and initial experimental evidence for cognitive training potential benefits for SUD [to a lesser extent for behavioural addictions (BAs)], there are also general questions regarding cognitive training underlying processes and their implications for clinical outcomes.

The interventions for EFs' rehabilitation and enhancement in addiction disorders can be described based on three different levels:

- the neurocognitive function (one or more) that is the target of the intervention,
- the type of intervention proposed (pharmacological, psychotherapeutic or tool-based).
- the population of individuals with addiction on which the intervention was applied, and it has been shown that it can bring benefits in terms of rehabilitation of cognitive functioning.

The objective of this chapter is to provide a discussion of the cognitive interventions dedicated to the rehabilitation and enhancement of EFs (in particular, cognitive bias, WM, inhibitory control, goal-directed behaviour, DM and metacognition) in addiction disorders. To date, the approaches that will be described in the next paragraphs have been mainly used for rehabilitation purposes of the EFs in addiction disorders, rather than from a preventive or strengthening perspective of these functions. Special attention will be given to the available neurophysiological and neuropsychological effects derived by the most frequently applied type of cognitive training in both SUD and BAs.

This contribution stands as an anticipation of the following chapters on the prevention and treatment for addiction disorders. Indeed, in Chap. 7, an overview of the main neuroscience methods that have been applied in the context of addiction disorders for rehabilitation and neuroenhancement purposes will be provided and will include an in-depth description of non-invasive brain stimulation (NIBS) techniques, such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and neurofeedback.

In the next two sections, the cognitive training dedicated to the rehabilitation of EFs in SUD and BAs will be described separately.

5.2 Cognitive Training for the Rehabilitation of EFs in SUD

The current preliminary evidence regarding the cognitive and clinical effects of cognitive training interventions adopted in SUD, as well as their neurobiological underpinnings, will be discussed below, with neurophysiological studies as a source of information (Luquiens et al., 2018).

Some common aspects shared by the training included in this chapter are: (1) the special attention dedicated to SUD, (2) their application in clinical studies on human participants, (3) the examination of their neurocognitive outcomes, (4) the wide use of computerized programmes and (5) the focus on EFs. Indeed, firstly, all the training trials described below mostly recruited SUD subjects with alcohol, methamphetamine, stimulant or opiate use disorders. Secondly, most studies adopted computerized programmes, which are likely to be cost-effective (Bickel et al., 2011; Fals-Stewart & Lam, 2010; Fals-Stewart & Lucente, 1994; Towe et al., 2021). Thirdly, these cognitive approaches are mainly tapping into the two complementary systems of addiction cited above, with a special focus on the EFs' treatment and their effects at the neurocognitive level.

The four main cognitive training interventions that have been identified are:

1. Cognitive Bias Modification (CBM),
2. Response inhibition training,
3. Working Memory Training (WMT) and
4. Goal Management Training (GMT).

They will be briefly described in the next paragraphs, and particular attention will be given to the resulting neurocognitive outcomes.

5.2.1 Cognitive Bias Modification (CBM) Training

CBM training aims to inhibit approach biases towards addiction stimuli (such as alcohol cues) through the formation of a new and more functional stimulus–response association, that is, the exposure to alcohol pictures associated with a motor avoidance response (for instance, pushing a joystick) (Wiers et al., 2010). In the context of SUD, CBM has been primarily applied to alcohol use disorder (AUD), owing to the employment of soft drinks (e.g., water) as a "neutral" alternative stimulus for alcohol cues.

This self-administered computerized training comprises two types of pictures (alcohol versus soft drinks) paired to two conditions (avoidance–push versus approach–pull). Participants are instructed to respond to pictures of alcohol making an avoidance movement (pushing the joystick) and to respond to pictures of soft drinks making an approach movement (pulling the joystick), for approximately 4–12 20-min training sessions (Eberl et al., 2013; Wiers et al., 2011). Sham training conditions require an equal number of approach and avoidance movements to both alcohol and soft drinks pictures (Wiers et al., 2011).

CBM is the only training that has been shown (1) to reduce alcohol use in the long-term, although this effect is moderate (Eberl et al., 2013; Wiers et al., 2011), (2) to reduce alcohol approach related biases and (3) to show better treatment outcomes at 1-year follow-up (Wiers et al., 2011).

5.2.1.1 Neurocognitive Findings

At the neurobiological level, CBM has been studied in the clinical field on subjects with AUD: Findings showed the CBM training works by down-regulating the activity in the medial prefrontal cortex (mPFC) and the amygdala, two regions that were shown to be involved in coding and learning process for emotional and motivational features of reinforcing stimuli, like alcohol or drug ones (Wiers et al., 2015a, b). Moreover, other top-down control mechanisms such as cognitive control and DM are mediated by the mPFC and the amygdala (Bechara et al., 2003; Ray & Zald, 2012). Also, a form of CBM (i.e., Computerized Approach Avoidance Training, CAAT) generated small-to-medium-sized cue-induced reductions in neural activation in the amygdala and prefrontal cortex (PFC) in adolescent cannabis users (Jacobus et al., 2018).

In a resting state based on electroencephalography (EEG) study, a general alpha synchronization increase was found in patients with AUD after the CBM protocol (Martínez-Maldonado et al., 2020). This increment in alpha phase synchronization could be explained as the neurobiological demonstration that alcohol-framed stimuli and avoidance response have been paired. Besides, after the protocol, AUD patients showed significant amelioration in the automatic responses, shown by a higher avoidance bias against alcohol-related stimuli in general, even if they were appetitive, aversive or not contextualized.

According to Washburn (2016), the critical process liable for the therapeutic effects of CBM appears to be the impulsive system, more than the executive systems, or at least not the domain of EFs which is captured by the Stroop test (cognitive control of the interference) (Washburn, 2016); however, this should be clarified by further additional studies in the field. Moderating factors for the CBM's effects are age and number of previous detoxifications: Older and less detox-exposed subjects are shown to getting more positive results after the treatment (Eberl et al., 2013).

Altogether, data suggest that CBM may lead to some positive results in individuals with AUD and cannabis users. The extent to which this training can be applied in other SUD is still to be determined, and it would benefit from a stronger adherence not only to the current methodological standards in Randomized Controlled Trial (RCT) design, but also to the systematic investigation of shared CBM protocols (Boffo et al., 2019).

5.2.2 Response Inhibition Training

The response inhibition programmes act by pairing addiction cues with "No-Go" signals, in order to retrain individuals to answer with avoidance actions to the specific types of salient cues (Houben et al., 2011a). Usually, in this self-administered computer-based training dedicated to AUD, eight alcohol stimuli are used: four water and four alcoholic drink (usually beer) pictures. Participants are told to press the space bar on a PC keyboard when a "Go" stimulus, like the letter "F", is shown

on the display, and to inhibit the motor response when a "No-Go" stimulus appears, the letter "P" for example.

During the training, water pictures are always associated with a "Go" stimulus, while beer pictures are associated with "No-Go" stimuli. In the sham condition, water pictures are paired with "No-Go" cue, and all the beer ones are paired with "Go" stimuli. Similar versions of this training have also been developed for other SUD (e.g., tobacco dependence; Staiger et al., 2018).

In two previous studies, this type of retraining programme was applied on a university sample of risky drinkers: Findings suggested that even one session of response inhibition training can reduce alcohol-approach actions and alcohol use (measured on the number of drinks consumed in the week after the training) in the individuals benefiting of this intervention (Houben et al., 2012, 2011a). Moreover, these studies showed that the critical function for the response inhibition training effects on AUD seems to be the impulsivity system moderation, and not the executive system empowerment, as shown by the results at the stop-signal task (Houben et al., 2012).

Similar results were obtained for individuals with gambling disorder: The response inhibition training was shown to be effective in reducing the approach bias towards gambling cues (Stevens et al., 2015a, b). Response inhibition training has been confirmed to reorient stimulus–action associations located in the same brain areas responsible for coding the value of the stimulus (striatum, mPFC), so it is plausible that the training works by rewiring action-value representations, at least in subclinical samples (Kim, 2013).

5.2.2.1 Neurocognitive Findings

Regarding neurophysiological findings, one session of response inhibition training has been related to an increment of the lateral PFC responsivity to "No-Go" stimuli in one EEG study involving a community sample of risky drinkers (Bowley et al., 2013).

The inferior frontal gyrus (IFG), the striatum and the subthalamic nucleus are known to be relevant brain regions involved in the control of inhibition (Aron et al., 2014; Morris et al., 2015). Response inhibition training via stop-signal exercises has been shown to induce increased IFG activation in the response preparation phase and decreased IFG activation in the response inhibition phase in healthy samples: These two neural changes were interpreted as behavioural improvement of inhibitory control ability (Berkman et al., 2014). Therefore, given the relevant and well-documented deficits in the IFG identified in SUD (Feil et al., 2010), stop-signal training deserves further study in the field of addiction.

Altogether, the currently limited neuroimaging evidence suggests that response inhibition training can enhance lateral PFC responsivity during "No-Go" or "stop" cues in community drinkers and healthy controls (Berkman et al., 2014; Bowley et al., 2013), although there is no neuroimaging evidence in clinical populations with SUD yet.

Despite inhibition deficits being well-documented in addiction disorders, there are limited data on the effectiveness of cognitive training exercises or initiatives aimed at improving inhibition skills in SUD. Recent research showed the possibility to prevent relapse in smokers by practicing a non-specific task of self-control (Muraven, 2010).

Extant findings suggest that response inhibition training has the potential for reducing alcohol use via changes in alcohol-related approach tendencies. Beneficial effects have only been shown in experimental studies (with a single session of training) among community samples, and thus its suitability for clinical populations remains to be tested.

5.2.3 Working Memory Training (WMT)

Generally, the WMT adopts exercises with progressive difficulty (like Digit Span, N-Back visual search and others) to reinforce information maintenance, manipulation and updating (von Bastian & Oberauer, 2014). Numerous computerized packages (Cogmed, PSSCogRehab, Cogpack and mHealth) are available for implementing specific and multicomponent approaches. An example of their application in intervention protocols dedicated to patients with SUD will be described below.

Indeed, this type of training has been tested on individuals addicted to alcohol, stimulant and opiate, and showed positive results with an amelioration on trained tasks performance, but mixed outcomes about the generalization of the effect to other tasks and clinical consequences were found (Bickel et al., 2011; Gamito et al., 2017; Houben et al., 2011b; Rass et al., 2015; Rupp et al., 2012; Snider et al., 2018).

WMT was shown to significantly reduced delay-discounting rates (i.e., impulsive choices) in psychostimulant users following Treatment as Usual (TAU) (Bickel et al., 2011) and in opiate-dependent users following methadone maintenance treatment (Rass et al., 2015) with moderate reduction of alcohol use in community drinkers, and stabilization of street drug use in methadone patients.

Regarding alcohol dependence, in a sample of heavy drinkers, Houben et al. (2011a) applied 20–25 sessions of Internet-delivered WM training (i.e., Cogmed's letter and digit span and visuospatial exercises), and the intervention led to interesting results in terms of improved performance at the trained tasks and behavioural measures (number of drinks after 1 week and after 1 month). WMT is suggested to be effective, especially in AUD subjects with strong motivational biases, suggesting a top-down "relaxation" effect on the impulsive system (Goldstein & Volkow, 2011).

5.2.3.1 Multicomponential Treatment Including WMT

In addition to specific WMT, two studies have applied multicomponent cognitive remediation programmes (Gamito et al., 2014; Rupp et al., 2012), which use WM exercises, along with attention, memory and planning/problem-solving training. Rupp et al. (2012) compared 12 sessions of computerized-based training (Cogpack) including WM, memory and attention exercises versus control (TAU) in AUD with moderate EF deficits. Individuals belonging to the cognitive training group showed amelioration's in tests of WM and general cognitive functioning (Mini-Mental Status Examination, MMSE), but not in tests of flexibility (e.g., Trail Making) or planning (e.g., Block Design). Gamito et al. (2014) compared 10 sessions of a mHealth (smartphone-delivered training, tapping into WM, attention and problem solving) versus TAU in patients with AUD, and found superior effects of the intervention on the EFs' battery (Frontal Assessment Battery), but not in general cognition (MMSE), or flexibility measures (Colour Trails Test, Wisconsin Card Sorting Test).

Recently, limited cognitive transfer affects WMT in heroin addicts (irrespective of current methadone treatment status); findings also suggest individual differences in training and transfer benefits dependent on baseline EF (Zhao et al., 2020). Overall, further evidence proves necessary for collecting the consistent effects of WMT on other EFs or on reduction of drug use (Khemiri et al., 2019) in clinical SUD populations.

5.2.3.2 Neurocognitive Findings

The neural markers of WMT have been partially examined in the context of SUD so far; instead, there is emerging evidence from numerous studies in healthy adults (for a review, see Buschkuehl et al., 2012), and in clinical populations with neurobiological overlaps with SUD, such as ADHD (Hoekzema et al., 2010; Stevens et al., 2015a, b). The available findings indicate that WMT is associated with more efficient activation of the dorsolateral prefrontal cortex (DLPFC), the ventrolateral prefrontal cortex (VLPFC) and the parietal cortex, and enhanced connectivity in the frontoparietal network (Jolles et al., 2013; Langer et al., 2013; Stevens et al., 2015a, b; Thompson et al., 2016).

Brooks et al. (2017) documented ameliorations in impulsivity in methamphetamine users after a computerized WMT (Brooks et al., 2017), as well as improvements in brain volume after the same programme (Brooks et al., 2016), but without a proper control group. Also, after 20 days of WMT, a group of drug abstainers showed an improvement in prefrontal EEG asymmetry scores and more spontaneous emotion regulation strategies compared with the control group (Deng et al., 2020). Despite this first interesting evidence at the neurocognitive level, the clinical significance of response inhibition and WM training-related changes in neurobiology remains to be explored.

5.2.4 Goal Management Training (GMT)

Usually, GMT adopts complex EF exercises, such as multitasking tasks or procedures highlighting the relation between decisions and future consequences (Levine et al., 2011), in order to functionally orient the behaviour according to previously determined goals. Moreover, in line with the idea that emotional factors are crucial to effective DM, these interventions could include additional emotional and motivational components. To our knowledge, limited studies have applied GMT in SUD and reported interesting effects at the EFs level (Alfonso et al., 2011; Casaletto et al., 2016; Gonçalves et al., 2014; Valls-Serrano et al., 2016).

An intervention combining GMT and mindfulness was applied in alcohol and stimulant outpatients following TAU (Alfonso et al., 2011). GMT consisted of a therapist-assisted community intervention including seven to eight 2-h sessions directed to sustained focus and EFs' improvements, as well as their translation to goal-related activities of real-life (Levine et al., 2011). In this case, the training also incorporated mindfulness to promote the switch between habit-based responses and goal-related activities. Confronted with TAU, the intervention was linked to substantial positive results in WM (measured by Letter Number Sequencing task), cognitive control (according to Stroop results) and DM (through the Iowa Gambling Task) (Alfonso et al., 2011; Verdejo-García et al., 2018).

Furthermore, self-reported abstinence was 25% higher in GMT participants than in TAU participants. The active ingredients in GMT are theoretically compatible with WM and cognitive control changes (Levine et al., 2011), and cognitive benefits seen in clinical trials using GMT in brain injury patients with EFs' deficits are similar (Novakovic-Agopian et al., 2011; Stubberud et al., 2013).

An innovative GMT including chess tasks was proposed to improve skills like planning and stimulus–outcome association in a sample of cocaine-addicted subjects who were following TAU (Gonçalves et al., 2014). This training consisted of ten 90-min therapist-assisted group sessions in which participants were advised on chess rules (to develop goal-directed behaviour) and chess strategy (to improve inhibition and reflection, as well as DM strategies, i.e., appropriate consideration of the implications of various moves/decisions). Authors also used motivational enhancing methods to relate chess activities to real-world goals and strategies. However, while the training increased WM span, there were no major changes in impulsivity, other memory or executive tasks.

Other two studies showed that polysubstance use patterns' participants enrolled in GMT performed significantly better than those in TAU after 7–8 weeks of training (Valls-Serrano et al., 2016), and people with methamphetamine use disorder have shown beneficial effects on EFs after GMT (Casaletto et al., 2016). Finally, recent studies suggested that GMT and Contingency Management training (donation of financial rewards associated with completion of cognitive training sessions) combined with CBT hold the potential to improve functional DM in people with addiction (Verdejo-García et al., 2018).

5.2.4.1 Neurocognitive Findings

Regarding neurocognitive findings, the neural signatures of the most popular GMT have been examined in one study among brain injury patients, in which individual differences in DLPFC responsivity were associated with treatment response (Chen et al., 2011). The neural blueprint of mindfulness meditation (one of the active ingredients of GMT) has been examined in one study among smokers, which has shown that this training is linked to increased resting-state activity in the VLPFC (relevant to goal maintenance) and the mPFC (relevant to feedback processing) (Tang et al., 2013). Altogether, the extant findings suggest that GMT may improve some EFs (WM, cognitive control and DM) in SUD (Verdejo-García et al., 2018). The extent to which these effects can be generalized to alcohol and drug use outcomes still needs to be determined.

Here, mindfulness was only reviewed when applied in combination with GMT, as the impact of mindfulness alone on the neurocognitive outcomes of interest will be discussed in the following chapter of this book (Chap. 6).

Despite being interesting, some other studies and interventions were not included in this discussion because of the poor relevance with the two systems of interest (Xue et al., 2012) or current insufficient evidence about their impact on neurocognitive outcomes (e.g., metacognitive training; Spada et al., 2015; Casaletto et al., 2016).

5.2.5 To Summarize

To summarize, based on the cognitive and neurocognitive findings described above, these four cognitive training can be grouped in two categories: the first one includes the CBM and response inhibition training, which have been shown to function by rewiring the mPFC and the amygdala and reorienting stimulus–action approach biases; and the second encompasses GMT and WMT, which have been linked to changes in stimulus–outcome representations, such as increased future-based delay-discounting and DM, and rewiring of the DLPFC and VLPFC (Verdejo-Garcia, 2016).

The above-mentioned cognitive training is generally successful in improving the qualified cognitive processes in SUD. Although the evidence is preliminary and more research is needed, the transfer to clinical outcomes is notable and potentially sound. To assess the importance of this line of research, replication studies and RCT with neuroscience-based mechanistic accounts are required.

5.3 Cognitive Approaches for the Rehabilitation of EFs in Non-substance-Related Disorder

5.3.1 Gambling Disorder

Shifting now the focus on BAs, cognitive impairments have been well-documented in gambling disorder, and even though effective treatment approaches exist (such as CBT), approximately 90% of the problem and pathological gamblers remain untreated (Meyer et al., 2011; Slutske, 2006). Given that cognitive distortions play a crucial role both in the development and maintenance of gambling problems, cognitive training targeting gambling-related biases may be particularly of interest and potentially effective in this clinical population.

So far, research literature focused more on cognitive training as a common treatment for SUD, rather than for BAs (Verdejo-Garcia, 2016). In a recent systematic review, Luquiens et al. (2018) stated that the use and efficacy data of the four cognitive training described above in individuals with gambling disorder are reduced and still missing.

Despite this gap in cognitive treatment, nowadays several candidate target functions for cognitive training are being studied, based on the most documented impairments of gambling disease, that is mainly inhibitory control (Bari & Robbins, 2013; Lubman et al., 2004; Morein-Zamir & Robbins, 2015; Verdejo-Garcia, 2016), DM (Kovács et al., 2017), and metacognition (Gehlenborg et al., 2021).

Regarding the adoption of response inhibition training (that exploits cues specifically related to the substance), at the methodological level, in gambling disorder, it seems that individual specificity of a gambling cue can be difficult to achieve in an experimental design conducted in the laboratory (Leyton & Vezina, 2012). On the contrary, due to their high incentive-salience, gambling cues have been found able to hinder the neural capabilities of the individual (Brevers et al., 2013).

Given this debate, it could be then useful to focus on rehabilitating cognitive function in other ways, perhaps without adopting gambling cues, and then concentrate on transferring the learned cognitive skills to everyday life, especially in gambling contexts. The viability of transferring benefits from training using non-specific stimuli (i.e., exercises unrelated to the drug or activity involved in the addiction process) has yet to be established both in SUD and BAs. However, considering the emotional relevance of gambling stimuli for individuals with gambling disorder and the strict connection between emotion modulation and EFs, future training programmes may integrate emotion regulation component during the training process dedicated to gamblers (Estévez Gutiérrez et al., 2014; Navas et al., 2017).

Moving on to possible current interventions that focus on metacognition, in a recent pilot study, Gehlenborg et al. (2021) examined the feasibility, acceptance and safety of a novel metacognitive training (MCT) for individuals with gambling problems. The training consists of multiple modules, including modules on metacognition, as well as modules on self-esteem and mood, debt regulation, urge to gamble and relapse prevention. The modules contemplate 60-min sessions including

exercises that allow participants to understand and work on distorted though. Despite results suggesting that self-report appraisal of Gambling MCT was good (Gehlenborg et al., 2021), no effects on neuropsychological and neurocognitive aspects were tested in this study, and future RCTs are needed for testing the efficacy of Gambling MCT.

Between the other challenges identified by Luquiens et al. (2018) for implementing cognitive training in gambling disorder, there are two main aspects related to neuroplasticity: The first concerns the possible underlying cognitive limitations due to the pathophysiology of the disorder, and, secondly, there are the maladaptive models of neural functioning that could be established and resistant in this population (Vinogradov et al., 2012). However, evidence of cognitive impairments in subjects with gambling disorder and data from the efficacy of cognitive training in SUD provide a reasonable foundation for using this treatment approach and designing controlled trials in the field. Some studies surprisingly reported an even higher level of impairment in some EFs and particularly in DM in people with gambling disorder than with AUD (Kovács et al., 2017). This should give a reason for particular optimism about the potential for progression through cognitive training programmes.

Finally, to answer the question of whether cognitive training should be an additional treatment or strategy in its own right, cognitive training may be used in conjunction with other techniques, especially those aimed at improving self-control. Some of the other methods and techniques that could be associated with cognitive training are mindfulness-based interventions (MBIs), repetitive transcranial magnetic stimulation (rTMS) (Tang et al., 2015) or medications that improve learning abilities (Bullock & Potenza, 2013; Skvarc et al., 2017), which are currently in the therapeutic pipeline for gambling disorder. However, once again aware of the wide treatment gap in gambling disorder (Gainsbury et al., 2014), computerized cognitive training as a single, non-face-to-face approach could be interesting on its own, and if successful, could present an interesting cost-efficacy solution.

5.3.2 Internet-Related Disorders

Concerning Internet-related disorders, research over the last decade has identified Internet Addiction (IA) as an often-unrecognized clinical disorder that impacts a user's ability to control online use to the extent that it can cause relational, occupational and social problems. However, recently, IGD has received more attention and has been included in the "Conditions for further studies" section of the DSM-5 (APA, 2013). Although much of the literature focuses on the psychological and social factors that contribute to IA, there are very little empirical data on specific treatment outcomes for this clinical group, even less on the neurocognitive effects of training.

Researchers have suggested using cognitive behavioural therapy (CBT) as the treatment of choice for IA, and addiction recovery, in general, has utilized CBT as part of treatment planning (King et al., 2017).

As an alternative, a relatively recent study focusing on the effects of the training on neurocognitive correlates proposed a combined treatment composed of electroacupuncture (EA) with psychological intervention (Zhu et al., 2012). It showed improvements in the cognitive function of IA patients at the electrophysiological level [in terms of Event-Related Potentials (ERP)] with reduced P300 latency and increased P300 amplitude in the EA group, while Mismatch Negativity amplitude increased in the controls: These mechanisms have been related to the speedup of cerebral discrimination on external stimulus and the enhancement of effective resource mobilization during information processing of the brain in the experimental group (Zhu et al., 2012).

More recently, the aim of Yao et al. (2017) study was to evaluate the efficacy of a group behavioural intervention incorporating reality therapy and MBI in reducing decisional impulsivity and IGD severity. Certain elements of the combined intervention, such as planning and commitment, are in line with the empowerment of DM training, as measured by delay discounting task. Nonetheless, the therapeutic emphasis on self-monitoring rather than "hands-on" activities, as well as the MBI intended as a post-training form of relaxation, renders the intervention similar to non-specific treatment or closer to CBT.

In general, the literature seems to suggest that psychosocial therapies (including CBT) for Internet-related disorders and pharmacotherapies for comorbid psychiatric or development disorders, more than cognitive training, have been effective at reducing the degree and symptoms of this disorder (Nakayama et al., 2017). Therefore, it is possible to conclude that for this type of BA the efficacy of cognitive training on the EFs, also at the neurocognitive level, is still to be tested, and new promising methods should be developed.

5.4 Tools for the Rehabilitation and Neuroenhancement of the EF in Addiction

A central assumption of addiction neuroscience is the presence of an imbalance between bottom-up cognitive systems, which are sensitized to the reward value of drug-related stimuli, and top-down executive and DM systems, which struggle to direct response selection according to long-term objectives (Bechara & Van Der Linden, 2005; Zilverstand et al., 2018) Currently, cognitive neuroscience provides various tools that can be used both for the rehabilitation and for functional neuroenhancement, from a preventive perspective, of these two systems (and in particular of the EFs) in the context of addiction.

In line with a neurocognitive architectural and functional perspective of addiction, it appears that retraining automated bottom-up processes by cognitive training and repeated exercise is adequate for SUD. And this is exactly what computerized cognitive training is aimed at: These interventions use software to retrain specific cognitive processes through repeated exercises, to restore cognitive functioning

through bottom-up paths. While to act directly on top-down-guided behaviour requires greater complexity to adapt cognitive strategies to the current context and future goals, and therefore in this case, it is more appropriate to envisage cognitive rehabilitation approaches (typically therapist-led) or a combination of multiple approaches (Harvey et al., 2018).

To provide an overview of the available tools for the rehabilitation and enhancement of EFs in addiction, it is possible to mention the following different approaches adopted to restore cognitive deficits: computerized cognitive training; cognitive rehabilitation; Virtual Reality (VR)-based training; psychotherapeutic approaches; pharmacological interventions and NIBS through neuromodulation techniques.

Current emerging trends suggest an integration of these distinct approaches based on the individual's phenotype and needs.

5.4.1 Computer-Based Cognitive Training in Addiction

Most of the cognitive training described above and dedicated to SUD usually adopted computerized programmes, which are likely to be cost-effective; however, research so far yielded mixed results.

Positive outcomes were found in patients with various SUD (cocaine, alcohol, opioids, stimulants and cannabis) with cognitive deficits (Fals-Stewart & Lucente, 1994), in SUD patients compared with controls (Fals-Stewart & Lam, 2010) and in patients with a stimulant use disorder (Bickel et al., 2011). On the other hand, after distinct sessions of the computerized training programmes, previous studies found no between-group differences in the cognitive performance in recently detoxified alcoholics (Peterson et al., 2002), adult treatment-seeking smokers (Loughead et al., 2016) and cigarette smokers (Adams et al., 2017).

Regarding the modalities in which the training is delivered, so far, numerous computerized packages mainly for cognitive training of EFs in SUD are available and include software like Cogmed [Pearson Education Inc. (cogmed.com)], PSSCogRehab (Psychological Software Services Inc., 1989, 2003) and Cogpack (Cogpack®Marker), or E-health and mHealth solutions. All the training packages can be self-administered, although the standard version of Cogmed also incorporates a coach to track the user's progress (Klingberg et al., 2005). In the studies previously mentioned, control interventions typically involve the same tasks without difficulty adjustments.

More recently, the feasibility and effectiveness of a web-based cognitive training programme to improve WM (48 daily sessions over 10 weeks) were tested in a sample of patients with cocaine user disorder (Towe et al., 2021). Overall, treatment completion and retention rates were high, and participant feedback indicated the intervention was acceptable: Results show that the intervention successfully reduced WM deficits in the experimental group relative to the controls (Towe et al., 2021).

In addition, this type of intervention paves the way for the application of computerized cognitive training delivered online.

5.4.2 Non-invasive Brain Stimulation Through Neuromodulation Techniques

With a view to neuroenhancement, Gladwin et al. (2016) proposed some interesting new directions for cognitive training research: The enhancement of training via tDCS, online training or gamification approaches (i.e., the use of gameplay elements) would increase motivation and could render CBM—and cognitive training in general—less repetitive and more reinforcing.

To deepen this theme, NIBS is a relatively emergent method that has some benefits over other addiction treatment options available in this field. Indeed, through the modulation of neuronal excitability, NIBS has the potential to target specific brain regions, allowing for the exploration of causal relationships between brain activity and behaviour. This capability may aid in improving the understanding of the physiological features underlying typical and atypical brain functioning (i.e., identifying potential biomarkers of diseases) and therapeutically restoring dysfunctional brain networks.

Due to its ability to modulate DM cognitive processes (Ouellet et al., 2015), modify neurophysiological circuitry (Clark et al., 2011; Hone-Blanchet et al., 2016) and decrease addiction symptomatology (Sauvaget et al., 2018) safely (Bikson et al., 2016) with significantly fewer associated adverse events than pharmacological treatments, NIBS may constitute an alternative option to traditional approaches adopted for addiction treatments (Kampman & Jarvis, 2015; Yip & Potenza, 2014).

So far, NIBS has been studied more extensively in SUDs (Coles et al., 2018; Trojak et al., 2017) and to a lesser extent in BAs (Gay et al., 2017; Lee et al., 2018), with studies focusing on feasibility approaches that were commonly modelled based on previous SUD results. Nevertheless, NIBS protocols may be effective for both disorders if the risk factors targeted are similar (for a review see Gomis-Vicent et al., 2019).

The two most commonly used forms of NIBS in addiction to date are tDCS and repetitive transcranial magnetic stimulation (rTMS) (Gomis-Vicent et al., 2019); nonetheless, even neurofeedback was demonstrated to be adequate for SUDs, for instance in AUD treatment (for a review, see Dousset et al., 2020). An overview of these neuroscience methods applied in the context of addiction disorders for rehabilitation and neuroenhancement purposes will be described in-depth in Chap. 7.

5.4.3 From Serious Games to VR-Based Approaches

Recent approaches to cognitive intervention in SUD have been taking advantage of what new technologies have to offer, and future promising approaches include the use of Serious Games and VR-based training.

Serious games supported by using tablets were previously used in recovering heroin addicts and consistent improvements in cognitive functioning for frontal

EFs, verbal memory and sustained attention, as well as some aspects of cognitive flexibility, DM and depression levels were reported between baseline and follow-up assessments (Gamito et al., 2017).

New technologies like VR could have the potential to improve the treatment of SUD and BAs (for a complete review, see Segawa et al., 2020). For instance, in the context of DM rehabilitation in addiction, immersive technology or life-long technology might help people visualize and emotionally connect with the long-term effects of hypothetical or real-life decisions. These technologies, in combination with "online" DM training, may be able to assist people suffering from addiction in correcting their short-term bias and strengthening their long-term DM (Verdejo-García et al., 2018).

Some experimental evidence has already been collected, in particular, after VR-based treatment, an increase in right frontal EEG alpha power in individuals with AUD was found and interpreted as a reduction of craving (Lee et al., 2009). Moreover, in IGD, higher connectivity from the Posterior Cingulate Cortex seed to the left middle frontal and bilateral temporal lobe was found (Park et al., 2016), suggesting the increase of balanced activation within the brain reward circuit by stimulating the limbic system.

Therefore, even novel technologies-based approaches, such as VR, hold potential for the enhancement of EFs, already displaying initial interesting results at the neurocognitive level.

5.5 Current Trends: From the Combination of Multiple Training Approaches to Precision Medicine

Given that people with SUDs and BAs have memory, attention, EFs and DM impairments, and that these deficits in higher-order EFs and DM can strongly predict relapse (Verdejo-García et al., 2018), the evidence previously reported in this chapter supports the assumption that cognitive training programmes aimed at reward-related appetitive biases, response inhibition, WM, attention and goal-based DM have the potential to help individuals with addiction-related cognitive deficits. Moreover, cognitive neuroscience and innovation technology provide various tools that can be used both for cognitive rehabilitation and for functional neuroenhancement in the context of addiction.

Within this framework, combining various neuroscience-informed interventions that synergistically tap into bottom-up versus top-down cognitive processes is one intriguing emerging approach (Spagnolo et al., 2020). In this perspective, there are at least four potential ways for approaches that consist of integrating:

1. cognitive training with existing evidence-based interventions;
2. cognitive training and physical exercise;
3. combination of two different cognitive training and
4. combining cognitive training with neuromodulation techniques.

Firstly, according to preliminary evidence, combining computerized cognitive training for general cognition (WMT or GMT) with Contingency Management (donation of financial rewards associated with completion of cognitive training sessions) seems to increase the intervention's beneficial effects on top-down cognitive skills (Bickel et al., 2011; Kiluk et al., 2017; Verdejo-Garcia et al., 2019). Whether this type of combination also leads to clinical improvement in terms of drug use and abstinence reduction is yet to be tested.

The second strategy is based on evidence that aerobic exercise regimens can minimize drug cues' salience (Conklin et al., 2017) and improve the availability of dopamine D2-type receptors in the striatum, which are associated to reward value and impulsivity. Integrating aerobic exercise with, for instance, inhibitory control training may thus have synergistic effects on cognitive control and craving.

The third approach consists of combining two different cognitive training (for instance, CBM and WMT), by carefully considering the intensity and duration of the interventions, for example, by alternating different training on different days and guaranteeing progressive difficulty, or by including both training into a single package (Verdejo-García et al., 2018).

The fourth integrated approach consists of combining cognitive training with neuromodulation techniques. When NIBS is used prior to or concurrently with a cognitive or behavioural intervention, it has the potential to increase and promote the intrinsic learning processes associated with those interventions (Cannizzaro et al., 2019). However, special attention should be given to the cognitive intervention proposed in combination with NIBS and the category of patients with addiction who could benefit from this treatment (Spagnolo et al., 2020).

Finally, another key emerging trend to address in future cognitive training and rehabilitation research is which elements of these interventions may work best for various patient subtypes, which coincides with phenotype-matched cognitive approaches for precision medicine.

In this perspective, Verdejo-Garcia et al. (2019) proposed a model in which the phenotyping of cognitive processes can lead to phenotype-matched cognitive and pharmacological approaches, as well as potentially improved SUD treatment outcomes. According to this model and current experimental evidence, they stated that CBM, WMT and GMT are best suited for patients with strong automatic biases, high impulsivity levels and poor DM skills, respectively, while pharmacotherapy and NIBS are increasingly helpful for addicted patients with high impulsivity and poor executive functioning. Finally, for patients with an extreme presentation of an identified phenotype, a meaningful combination of cognitive and biological approaches (e.g., WM training and left DLPFC stimulation for highly impulsive patients) could be particularly useful (Verdejo-García et al., 2018).

5.6 Conclusions

The available neurocognitive approaches described above have been used to date for the rehabilitation of EFs in addiction disorders, rather than from a preventive or strengthening perspective.

To summarize, common aspects between these training were the special attention dedicated to SUD, their application in clinical studies of human participants, the examination of their neurocognitive outcomes, the wide use of computerized programmes and the focus on EFs. Specifically, the cognitive training adopted in SUD can be clustered in two classes: CBM and response inhibition, which have shown to operate via reorientation of stimulus–action approach biases and rewiring of the mPFC and the amygdala; WMT and GMT interventions, which have been associated with improvements in stimulus–outcome representations, for example, increased future-based delay-discounting and decision-making, and rewiring of the DLPFC and VLPFC (Verdejo-Garcia, 2016).

Despite cognitive impairments being well-documented in BAs (especially in gambling disorder), the use and efficacy data of the four cognitive training described above in gambling disorder are reduced and still missing (Luquiens et al., 2018); while for Internet-related disorders, CBT seems to be the treatment of choice (King et al., 2017).

Currently, cognitive neuroscience and innovation technology provide various tools that can be used both for cognitive rehabilitation and for functional neuroenhancement in the context of addiction. The tools for the rehabilitation and neuroenhancement of the EF in addiction described in this chapter mainly include computer-based cognitive training, NIBS through neuromodulation techniques and other promising tools such as serious games and VR-based approaches.

As methodological considerations, there is a need for RCT: Proper control groups with placebo conditions should be implemented; assessment of efficacy should be transversal and include clinical and neuropsychological assessments to give information of underlying mechanisms of action. Moreover, transversal assessment on the efficacy of these interventions should include neuropsychological and neuroimaging/neurocognitive evidence.

To conclude, future neuroscience research on these approaches, either a combination of these interventions, is needed both in SUD and especially in BAs. The combination of various neuroscience-informed interventions that synergistically tap into bottom-up versus top-down cognitive processes on the one hand, and the phenotype-matched cognitive approaches for precision medicine, on the other hand, are two intriguing emerging approaches for finding the best way to empower EFs in addiction.

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Chapter 6
Mindfulness-Based Interventions (MBIs) as a Way for Treating EFs in Addiction-Related Disorders

Michela Balconi and Laura Angioletti

6.1 An Introduction to Mindfulness-Based Interventions (MBIs)

Mindfulness is considered in Western culture as a unique type of mental training based on self-observation and awareness practices that are cantered on the present and require deliberate intentional focusing on and acceptance of one's bodily sensations, mental states and emotions, as well as mental non-judgement and moment-by-moment living (Kabat-Zinn, 2003). It enables one to actively perceive and consciously recognize one's mental states as well as the physiological reactions that go along with them (Keng et al., 2011).

Mindfulness has recently been demonstrated as a way to improve individual psychological wellness in both healthy and clinical populations (Balconi et al., 2017b; Crivelli et al., 2019c; Keng et al., 2011). Furthermore, prior research has shown the effectiveness of mindfulness training on a variety of cognitive functions, including attention self-regulation and sustained attention (Balconi et al., 2019b; Crivelli et al., 2019c), the prevention of working memory decline (Jha et al., 2017), reduction of cognitive reactivity, mental rumination (Raes et al., 2009) and physiological reactivity to stress (Balconi et al., 2018; Crivelli et al., 2019c). Therefore, mindfulness training holds potential for impacting on executive functions (EFs) also in the field of our interest, that is, addiction-related disorders.

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In this chapter, Mindfulness-Based Interventions (MBIs) will be described considering their application to addiction-related disorders, substance use disorder (SUD) as well as Behavioural Addictions (BAs). Special attention will be given to the therapeutic mechanisms of MBIs as a treatment for addiction and on the neurocognitive correlates on which MBIs impact. Therefore, where available, neurophysiological evidence of the effects of MBIs' application on EFs in addiction-related disorders will be reported.

The reason for focusing on neurocognitive correlates of the intervention is that they constitute the target neurophysiological basis for protocols that combine neuroscientific tools with MBIs for boosting EFs in addiction-related disorders. In fact, the last paragraphs of the chapter will discuss the proposal of combining the application of MBIs supported by neurofeedback devices, describing how to promote behavioural self-regulation through the self-regulation of cortical activity.

6.2 MBIs for Addiction-Related Disorders

In the field of substance addictions, current developments derived from addiction neuroscience studies have advanced hand in hand with a growing interest in the ancient mental training practice of mindfulness meditation, conceived as a potential treatment for addictive behaviour. The active introduction of mindfulness strategies into well-established behavioural intervention practices, such as Mindfulness-Based Stress Reduction (MBSR) (Kabat-Zinn, 1990) or Mindfulness-Based Cognitive Therapy (MBCT) (Segal et al., 2002), ignited this interest and accelerated the growth of research studies that test the efficacy and clinical outcomes of this mental practice.

Initially, in the clinical field, standardized mindfulness-based interventions (MBIs) were developed with the aim of minimizing emotional distress, and in fact, they were shown to be effective and comparable to other active treatments for psychiatric disorders and symptoms (Goldberg et al., 2018). More recently, MBIs like Mindfulness-Based Relapse Prevention (MBRP) (Bowen et al., 2014) and Mindfulness-Oriented Recovery Enhancement (MORE) (Garland et al., 2012b) have been specifically designed to target the processes that underpin addiction.

But let us briefly see what an intervention based on mindfulness practices consists of before conceiving of its application as a means of targeting mechanisms of addiction.

MBIs teach practices that elicit the state of mindfulness, which is described as a state of metacognitive awareness characterized by attentive and non-judgemental monitoring of moment-to-moment cognition, emotion, sensation and perception without dwelling on past or future thoughts, but only with a focus on the present (i.e., in the here and now).

Mindfulness practice is thought to consist of two main components: focused attention and open monitoring (Lutz et al., 2008; Vago & Silbersweig, 2012). During the practice of focused attention, the attention is kept on a sensory object (often the

sensation derived from one's breath, also interoceptive and proprioceptive body sensations or external visual points can be used), while in the meantime, the person recognizes distracting thoughts and emotions and then turns away attention from them, returning with the focus on the sensory object. Usually, focused attention practices consist of exercises that often precede the practice of open monitoring in which instead individuals observe both the emergence of mental contents and the field of awareness in which these contents arise (Lutz et al., 2008).

As a metacognitive state of awareness, open monitoring involves tracking the content of consciousness while reflecting on the process or quality of consciousness itself. By exposing the transience of any specific substance of consciousness, this type of mindfulness practice is thought to minimize emotional reactivity. The neurocognitive models at the basis of the processes of focused attention and open monitoring mapped these practices back to a meditation cycle that involves the interaction of various cognitive processes, including sustained attention, attention reorientation, conflict monitoring, online information retention in working memory, inhibitory control and emotion regulation (Vago & Silbersweig, 2012). Furthermore, morphometric neuroimaging meta-analysis studies indicate that a higher dose of mindfulness meditation practice is linked to neuroplastic changes in brain structure (Fox et al., 2014), as will be described below.

Mindfulness conceived as a disposition or a trait component is defined by the ability to remain non-reactive and tolerate distressing thoughts and emotions; observe the interoceptive and exteroceptive experience, and distinguish between emotional states, as well as being conscious of automatic reactions (Baer et al., 2006). In previous addiction studies, trait mindfulness has been linked to improved cognitive control capacities (Anicha et al., 2012), is significantly inversely associated with substance use (Karyadi et al., 2014) and craving (Garland et al., 2014b) and is positively linked to the ability to disengage attention and recover autonomic function after exposure to addiction-related cues (Garland, 2011; Garland et al., 2012a), thus resulting as a remedy to addiction. If compared to mindfulness disposition, which is associated with cognitive and behavioural flexibility, addiction may be defined as *mindlessness* (Langer, 1992) since it is characterized by conditioned or stereotyped responses that are performed spontaneously without conscious volition or strategic consideration for distal outcomes.

As anticipated, the most relevant MBIs applied in the context of addiction (e.g., MBRP, MORE, awareness training dedicated to smokers) were designed after the first generation of "classic" mindfulness-based therapies such as MBSR and MBCT, both in terms of format and realization.

MBIs for addiction are typically multiweek treatments (8 weeks in length) administered in a community therapy environment, as group intervention. Participants are led through various mindfulness activities, such as mindful breathing and body scan meditations, by a professional clinician once a week. During a subsequent group meeting, these in-session mindfulness activities are debriefed, and new psychoeducational content is usually introduced. Experiential exercises are often used in sessions to reinforce the mindfulness concepts that have been taught didactically. Therapeutic homework is provided to participants, which includes

formal and informal mindfulness activities as well as tasks to self-monitor symptoms including craving and negative affect.

The differences between existing MBIs for addiction are the styles of mindfulness practices taught in the classes, the way these practices are conducted and debriefed (for instance, MBRP uses transparent, non-directive inquiry, while MORE uses a directive approach with a high degree of positive reinforcement), the duration of at-home mindfulness practice sessions and the basic psychoeducational material used.

MBIs for addiction are typically designed to target pathogenic factors involved in addiction by focusing on addictive habits (e.g., mindfulness of craving) and exploring how to use mindfulness skills to deal with addiction in daily life. Moreover, MBIs are designed to train a set of cognitive, affective and psychophysiological processes integral to self-regulation and reward processing, based on neurocognitive processes which will be explored in the next paragraph.

6.3 Mechanisms and Neurocognitive Correlates of MBIs as a Treatment for Addiction-Related Disorders

MBIs are considered to train mechanisms critical to the self-regulation of addictive behaviour and functions typically belonging to the family of EFs, such as attentional re-orientation, metacognition, reappraisal and inhibitory control, via focused attention and open monitoring mindfulness practices (Vago & Silbersweig, 2012).

One of the most recent models conceptualizing neurocognitive correlates of MBIs in addiction (Garland et al., 2014a) proposed MBIs as a type of mental training adequate to strengthen a variety of neurocognitive mechanisms that become dysregulated during the addiction cycle (Garland et al., 2014a).

MBIs can be conceived in this light as training for restoring the integrity of prefrontally mediated cognitive control networks that are weakened and have become atrophied as a result of continuous substance use and that have been negatively influenced by drug-related signals and cravings during the addiction process. With the enhancement and restoration of functional cognitive control, obtained through awareness exercises, MBIs have shown that they can increase the functional connectivity in fronto-striatal circuits, that is, between the prefrontal networks (involved in top-down processes) and the limbic-striatal brain circuits involved in bottom-up processing of reward and motivation (Garland et al., 2014a): This cortical–subcortical loop constitutes the physiological substrate through which MBIs can deautomatize addictive behaviour.

In a review describing the current state of the field (Garland & Howard, 2018), the specific neural functional mechanisms of MBIs for addiction and experimental evidence of their effectiveness have been collected.

By increasing fronto-striatal circuits' activity in a goal-directed manner, MBIs may enhance fundamental neurocognitive resources that in turn can be used to modulate a variety of mechanisms implicated in addiction, encompassing reward

processing, EF, drug cue-reactivity, stress reactivity, negative affects states, automatic habit behaviours and thought suppression.

Garland and colleagues (2014a) model of mindfulness-centred regulation posits that MBIs ameliorate addiction-related behavioural mechanisms by enhancing functional connectivity:

- within a "top-down" brain network subserving metacognitive attentional processes [portions of the PFC (dorsolateral and medial PFC), orbitofrontal cortex (OFC), dorsal, rostral and subgenual Anterior Cingulate Cortex (dACC, rACC, sgACC), parietal cortex]
- between this metacognitive attentional control network and "bottom-up" brain structures implicated in automaticity, memory consolidation, interoception and hedonic regulation [Ventral Striatum (VS), dorsal striatum, amygdala and anterior/mid insula].

If functional connectivity within and between these neural circuits is improved, individuals with addiction disorders may become able to self-regulate addictive urges and restructure reward mechanisms to promote a more functional and goal-oriented behaviour.

Recently, Brewer (2019) underlined that understanding core brain systems, including the role of the OFC in reward value comparison as part of the learning system, may give fresh insight into not only the automaticity and perpetuation of addictions but also how they can be overcome (potentially without relying on cognitive control). Among the various alternatives to be able to defuse these automatic loops, it is interesting to note that mindfulness and awareness practices have been cited by the author as particularly critical in unlocking the power of reward-based learning to change addictive habit patterns, perhaps actively acting on the OFC (Brewer, 2019).

Although in the clinical setting, understanding the neurocognitive mechanism underlying a type of treatment is not necessary to establish whether a given treatment modality is an empirically supported intervention, it is possible to recognize that understanding the underlying basis of the link between mindfulness and neural correlates in addiction can inform the refinement of MBIs to produce larger clinical effects and additional long-term therapeutic benefits.

6.3.1 Neurophysiological Evidence of MBIs in SUD

Some main effects of MBI on SUD at the neurocognitive and neurophysiological level will be described in the following paragraphs. An emerging body of research suggests that MBI acts mainly on craving, reward mechanisms and stress in different SUD populations, and below we will report some of the results mainly observed in individuals with addiction to tobacco, alcohol and opioids.

6.3.1.1 Neurophysiological Evidence of MBIs on Cue-Induced Craving

Firstly, in individuals with tobacco dependence, one way that mindfulness may facilitate smoking cessation is through the reduction of craving towards smoking cues.

Westbrook et al. (2011) tested whether mindful focus can minimize self-reported and neural indicators of cue-induced craving in treatment-seeking smokers. While undergoing functional magnetic resonance imaging (fMRI), 47 meditation-naive treatment-seeking smokers (12-h abstinent from smoking) viewed and rated smoking and neutral images. Participants received the instruction to watch the pictures in two different conditions: passively or with focused attention (i.e., mindful condition). Findings indicated that mindful attention reduced the self-reported craving to smoking images and reduced neural activity in a craving-related region of sgACC. Moreover, a psychophysiological interaction analysis revealed that mindful attention reduced functional connectivity between sgACC and other craving-related regions compared to passively viewing smoking images, suggesting that mindfulness may decouple craving neurocircuitry when viewing smoking cues. These results provide an initial indication that mindful attention may describe "bottom-up" attention to one's present moment experience in ways that can help reduce subjective and neural reactivity to smoking cues in smokers.

6.3.1.2 Neurophysiological Evidence of MBIs on Reward Processing

Regarding reward processing, addiction neuroscience models posit that recurrent drug use increases reactivity to drug-related cues and blunts responsiveness to natural rewards, propelling a cycle of hedonic dysregulation that drives addictive behaviour.

In this regard, recently a pilot feasibility study examined the effects of MORE on fronto-striatal reward processes among cigarette smokers (Froeliger et al., 2017). A total of 30 healthy adults participated in a 10-week study testing MORE versus a control group (CG). All participants underwent two fMRI scans: pre-training and after 8 weeks of MORE. Emotion regulation (ER), smoking cue reactivity (CR) and resting-state functional connectivity (rsFC) were assessed at each fMRI visit; smoking and mood were assessed throughout. As compared to the CG, MORE significantly reduced smoking and increased positive affect. MORE participants evidenced decreased CR-BOLD response in VS and ventral prefrontal cortex (vPFC) and increased positive ER-BOLD in VS and vPFC. Importantly, ER was correlated with smoking reduction and increased positive affect. These findings provide preliminary evidence that MORE may facilitate the restructuring of reward processes and play a role in treating the pathophysiology of nicotine addiction.

Also, dysregulated processing of natural rewards may be a central pathogenic process in the aetiology and maintenance of prescription opioid misuse and addiction among chronic pain patients. In this framework, Garland et al. (2014a, b) examined whether a MORE intervention could augment natural reward processing as

indicated by event-related brain potentials (ERPs). Participants were chronic pain patients at risk for opioid misuse who were randomized to 8 weeks of MORE or a support group control condition. ERPs to images representing naturally rewarding stimuli (e.g., beautiful landscapes, intimate couples) and neutral images were measured before and after 8 weeks of treatment. Analyses focused on the late positive potential (LPP), an ERP response in the 400–1000 ms time window thought to index allocation of attention to emotional information. Treatment with MORE was associated with significant increases in LPP response to natural reward stimuli relative to neutral stimuli which were correlated with enhanced positive affective cue responses and reductions in opioid craving from pre- to post-treatment. Findings suggest that cognitive training regimens centred on strengthening attention to natural rewards (such as this form of mindfulness) may remediate reward processing deficits underpinning addictive behaviour.

More recently, Garland et al. (2019) assessed whether MORE could restructure reward responsiveness from valuation of drug-related reward back to the valuation of natural reward. Before and after 8 weeks of MORE or a support group control, prescription opioid users viewed opioid and natural reward cues while an electroencephalogram biomarker of target engagement was assessed. MORE was associated with decreased opioid cue reactivity and an enhanced capacity to regulate responses to opioid and natural reward cues (as demonstrated by heightened LPP responses). Increased positive affective responses to natural reward cues were associated with decreased craving and mediated MORE's therapeutic effects on opioid misuse. Garland's series of randomized experiments provide the first neurophysiological evidence that an integrative behavioural treatment can remediate hedonic dysregulation among chronic opioid users.

6.3.1.3 Neurophysiological Evidence of MBIs on Stress Reactivity

Stress together with negative affect is a known contributor to drug use and relapse, and several known treatments for addictions include strategies for managing them. Kober et al. (2017) administered a well-established stress provocation during fMRI to 23 participants who completed either mindfulness training (MT) or a specific form of cognitive-behavioural treatment (CBT) for smoking cessation. Across the entire sample, authors found that stress reactivity in several brain regions including the amygdala and anterior/mid insula was related to reductions in smoking after treatment, as well as at 3-month post-treatment follow-up. Moreover, conjunction analysis revealed that these same regions also differentiated between treatment groups such that the MT group showed lower stress reactivity compared to the CBT group. This suggests that reduction in stress reactivity may be one of the mechanisms that underlie the efficacy of MT in reducing smoking over time. The findings have important implications for our understanding of stress, the neural and psychological mechanisms that underlie mindfulness-based treatments and for SUD treatments more broadly.

Finally, it is worth noticing that mindfulness is associated with attentional and autonomic control, two neurocognitive functions that are compromised in addiction, and as a trait component, mindfulness trait differs among meditation-naïve practitioners. According to Garland (2011), higher trait mindfulness is associated with less difficulty resisting the urge to drink (measured by an attentional bias protocol) and greater high-frequency heart rate variability (HFHRV; index of autonomic reactivity) recovery from stress-primed alcohol signals in alcohol-dependent inpatients After statistically controlling for the correlation of mindfulness and perceived difficulty resisting drinking urges, authors found the relationship between mindfulness and HFHRV recovery was partly mediated by attentional disengagement from alcohol cues. Alcohol-dependent inpatients with higher mindfulness traits seem more able to disengage their attention from alcohol cues, a signal which predicts the degree of HFHRV recovery from such cues. As a result, it is conceivable that trait mindfulness may be used to measure cognitive control over appetitive reactions, as shown by better attentional and autonomic regulation of stress-induced alcohol cue reactivity.

This evidence suggests that MBI can act mainly on craving, reward mechanisms and stress in different SUD populations (tobacco, opioids users and alcohol patients), demonstrating positive changes at the neurocognitive, electrophysiological level and correlations with autonomic activity supporting cognitive and emotional functioning. The focus of the chapter is dedicated to the effects of MBI on EFs; therefore, the next paragraph will offer an overview of some studies that demonstrate how this type of intervention can also have an impact on EFs in SUD.

6.3.2 Evidence of MBIs Application on Executive Functioning in SUD

Below a description of some studies that have shown evidence that MBIs can be considered a valid application for the treatment of FE in the SUD (specifically poly-substance users and smokers) will be provided. Indeed, MBIs can improve EFs like self-control over automatic behaviours, decision-making and reaction inhibition, which are critical for reducing drug use and maintaining abstinence, by improving top-down cognitive control (Garland & Howard, 2018).

Starting with special attention towards the neurophysiological correlates of the efficacy of MBI for addictions, there is preliminary evidence that MBIs for addiction increase activation in brain regions implicated in self-regulatory EFs: A small randomized controlled trial (RCT) showed that 2-week mindfulness training (2 weeks per 5 h in total) was associated with a significant reduction in smoking coupled with increased resting-state activity in the ACC and mPFC (two brain regions related to self-control and for which regional cerebral blood flow was found to be reduced in cigarette smokers) (Tang et al., 2013). Such increased prefrontal activation might facilitate mindfulness-induced deautomatization of addictive

responses. This study is particularly interesting because it combines neurocognitive and neuroscientific aspects in demonstrating the effectiveness of MBIs on EF. More recently, in another clinical trial, mindfulness-based addiction treatment significantly improved smoking abstinence by decreasing attentional regulation issues, anxiety levels, craving and dependence, and boosted self-efficacy for managing negative affect without smoking (Spears et al., 2017).

In line with the emerging approaches for finding the best way to empower EFs in addiction (mentioned in Chap. 5), two relatively recent studies tried to combine MBI with cognitive training.

Specifically, the combination between MBI and GMT (an interactive programme aimed at improving participants' organization and ability to achieve goals; Levine et al., 2011) was applied to improve attentional scanning and "reading" of emotional signals involved in adaptive decision-making, and mindfulness was added to GMT to facilitate the switching between habit-based responses and goal-related tasks. Results proved significant ameliorations in EFs (measured by neuropsychological tests), including working memory, selective attention/response inhibition and decision-making skills following mindfulness training relative to TAU in polysubstance users (Alfonso et al., 2011). Present findings on the efficacy of combined GMT and MBI for polysubstance users were confirmed by a subsequent pilot RCT in laboratory-based tasks and ecologically valid measures of decision-making (Valls-Serrano et al., 2016).

Although these results are promising, further and more robust RCTs with MBRP either MORE structured intervention are needed, in order to determine the differential contribution of "cognitive" GMT exercises and mindfulness "affective" exercises in combined therapeutic and neurobiological pathways and to test the real effectiveness of MBI on EFs in SUD.

6.3.3 Experimental Evidence from MBIs Applied to Behavioural Addictions (BAs)

In the last 15 years, MBIs have also been applied in populations of individuals with BAs. In general, to date, there seems to be scarce literature on the neurophysiological effects of MBI in these populations, and the focus is more on clinical results than on the specific effects that can be grasped on EFs. This constitutes a gap in the literature but also a great development opportunity for applying this practice in BAs.

In fact, the application of MBI in SUD populations has so far proved effective in reducing craving, reward sensitivity, stress reactivity and negative affect on a general level; while for EFs, MBIs may act on the deautomatization of addictive responses, decision-making, reaction inhibition, self-control and attention regulation. It would be of great interest to verify whether these effects on the EFs can also be observed in populations of individuals with non-substance-related disorders, such as GD and IGD.

Concerning GD, recent systematic reviews highlighted that gambling severity, urge of playing and financial outcomes were primary outcomes and positive results of studies focusing on MBI effectiveness in GD (Maynard et al., 2018; Sancho et al., 2018). Previous investigations have revealed that dispositional mindfulness is related to less severe problem gambling outcomes and that psychological distress, overconfidence, risk-taking willingness, myopic focus on reward and ego involvement may act as mediators in this relationship (de Lisle et al., 2012). Moreover, the literature indicates that the inverse relationship between dispositional mindfulness and psychological distress may be mediated by factors such as values clarification; emotional, cognitive and behavioural flexibility; non-attachment; emotion dysregulation/distress intolerance; thought suppression and rumination (de Lisle et al., 2012).

Regarding IGD, as a broad category encompassing gaming, the internet and smartphone addiction, limited studies have been applied before to test whether MBIs can be a valid approach for reducing symptoms and severity of IGD. They found MBIs may lead to reductions in IGD severity, craving for video game playing (Li et al., 2018), maladaptive cognitions associated with gaming (Li et al., 2017), delay discounting rate (Yao et al., 2017) and time spent using the smartphone (Lan et al., 2018). Interestingly, a previous study demonstrated that mindfulness and self-control mediate the relationship between stress and Internet Addiction (IA). Indeed, stress had a direct boosting effect on Internet addiction, but both mindfulness and self-control mediated this relationship. Specifically, mindfulness demonstrated a dual mediating effect on IA by enhancing self-control, thereby lowering the risk of IA (Song & Park, 2019).

So far, findings provide support for MBI in the treatment of GD and IGD. However, these results are necessarily tentative, limited by the number and quality of eligible studies, and differing conceptualizations of mindfulness.

6.4 Combining Neuroscientific Tools with MBIs for Boosting EFs in Addiction-Related Disorders

As already anticipate in Chap. 5, cognitive neuroscience and innovation technologies offer a variety of resources relevant and precious for both cognitive treatments and functional neuroenhancement of addiction-related disorders. In this context, the combination of several interventions based on neuroscience, which synergistically impacts bottom-up and top-down cognitive processes, turns out to be an approach with potential interesting long-term clinical outcomes and on which neuroscientific research is also heading (Spagnolo et al., 2020).

Indeed, combining cognitive (or mental) training with neuromodulation techniques may enhance the training impact at the neurocognitive level and over time. When non-invasive brain stimulation (NIBS techniques) is implemented before or alongside a cognitive or behavioural intervention, it can enhance and facilitate the inherent learning mechanisms associated with such interventions (Cannizzaro et al., 2019).

Therefore, in the next paragraphs, a possible approach of combining MBI with neuromodulation tools will be described and proposed for the field of addiction neuroscience. Among the various NIBS techniques now available, the focus will be on neurofeedback (NF) techniques.

6.4.1 Neurofeedback Interventions and Wearable Devices

Before discussing the effects of combined MBI + NF interventions in the field of addictions, let us start with a brief description of NF.

NF is a technique based on the principle of operating conditioning that allows individuals to learn to self-regulate their cortical activity, and that has been demonstrated to be efficacious in cognitive enhancement on healthy individuals (Gruzelier, 2014). The basic principle of NF could be conceived as a loop. Indeed, NF measures the individual brain activity, processes the brain patterns of interest (e.g., alpha waves for relaxation) and provides the user with audio or video feedback stimuli related to the activity of processed cortical rhythms. Briefly, NF devices collect electroencephalographic (EEG) brain waves signal and effectively provide real-time feedback on the person's mind–body state activity (Gruzelier, 2014).

Compared to traditional NF, the new NF wearable device added value lies in the high usability, low cost and portability. NF wearable devices' reliability in quality signal was previously compared with EEG signal and demonstrated good quality standard and precise feedback (Balconi et al., 2017b; Bhayee et al., 2016). Nowadays wearable devices provide actual opportunities to easily make even naïve practitioners access to implicit markers of their internal neural and bodily states (e.g., EEG rhythms) and process such information at the conscious level. Data on the outcome and efficacy of a mental training protocol supported by these wearable brain-sensing devices showed the devices helped practitioners to train and optimize the efficiency of attention regulation, control and focusing skills. These effects are marked by a reduction of response times during complex cognitive tasks without loss of accuracy. Moreover, at the central level, an enhancement of ERPs marking early attention orientation and cognitive control was detected (Balconi et al., 2019b).

The adoption of wearable neurotechnology could be a feasible way to apply neurocognitive enhancement in the company, given the devices are practical, easy-to-use, the feedback interface is user-friendly and the system is adequate for professionals of all levels.

To summarize, the main advantage of the NF technique is that it critically grounds on the active role of the participant (since it applies the principles of operant conditioning), and, in this way, it promotes plasticity and cognitive empowerment by actively training participants' self-awareness and active control over physiological correlates of cognitive skills. In contrast, NIBS is based on externally induced stimulation or modulation of ongoing neural activity and does not necessarily require the active engagement of the stimulated individual (Enriquez-Geppert et al., 2014). It has been suggested that it is exactly such a peculiar feature of NF

empowerment interventions that might have additional results on long-term retention of training effects since the participants are directly involved in finding and consolidating personalized strategies to intentionally modulate their neurophysiological activity.

What is of interest to us to underline this point is that the NF technique has previously been applied in populations with SUD and has proven to be an add-on tool in the management of the disorder. In these studies, participants are usually presented with either fMRI- or EEG-based feedback derived from select relevant brain processes. For instance, a real-time fMRI-NF study on treatment-seeking smokers benefiting from NF showed a decreasing activity in functionally defined regions involved in craving (ventral ACC) and increasing activity in regions involved in "resisting" (dmPFC). Clinically based rtfMRI-NF studies usually employ this imaging modality to train participants' behavioural self-regulation in order to decrease drug craving and, as a result, the frequency of the substance use (for a review on rtfMRI-NF research on individuals consuming nicotine, alcohol and cocaine, see Martz et al., 2020). Another approach consists of EEG-NF protocols applied in AUD (Dousset et al., 2020; Peniston & Kulkosky, 1989) and cocaine addiction (Horrell et al., 2010; Stotts et al., 2007). Protocols applied in AUD were shown to enhance the cognitive abilities required to maintain abstinence, with a focus on inhibition and attentional skills (for a review, see Dousset et al., 2020).

In addition to neuromodulation and neurophysiological self-control techniques, other studies have observed the efficacy of mental awareness-based practices on neurocognitive improvements, such as MBI combined with NF. Indeed, in recent years, the strive to improve personal potential and efficiency of cognitive functioning also led to the revival and the renewed diffusion of mental training activities. A growing literature on the effects of mental training and meditation practice highlighted their potential for modulating overt behaviour and covert psychophysiological activity (Quaglia et al., 2016) and for inducing short-term and long-term empowerment effects on cognitive and emotion regulation skills (Balconi et al., 2017a, b; Keng et al., 2011). Special attention to this relatively new approach will be given in the next paragraph.

6.4.2 MBIs and Neurofeedback Technique in Addiction-Related Disorders: State of the Art and Proposals

Among the approaches that involve the combination of MBIs and neurofeedback technique, it is possible to distinguish two different modalities of application of the intervention: Indeed, the NF system can be applied "off-line", that is, before and after the MBI, and "online", that is simultaneous with mindfulness practice.

About the first modality, a recent still ongoing project will use MBRP in AUD to improve the efficacy of a real-time fMRI-NF intervention targeting the VS, which is

a brain region centrally involved in cue reactivity to alcohol-related stimuli (Weiss et al., 2020).

To better understand the intervention, a brief description of the design is provided here. AUD patients will be randomly assigned to one of four groups: Two of those groups will receive TAU, and the other two groups will receive five sessions of MBRP prior to the NF intervention. These two groups (TAU and MBRP) will further each be divided into two subgroups, who receive either rtfMRI-NF from the VS with the instruction to down-regulate it (experimental group) or they receive feedback from the control region which is the auditory cortex (CG). All groups will receive two fMRI sessions and three rtNF sessions in a double-blind manner and will regulate either the VS or the auditory cortex as a control region. After the last fMRI session, the participants will be followed up monthly for a period of 3 months for an assessment of the relapse rate and clinical effects of the intervention. The results of this study will give further insights into the efficacy of rtfMRI-NF intervention for the treatment of AUD. Additionally, the study will provide further insight into neurobiological changes in the brain caused by the NF intervention as well as by the MBRP. The outcome might be useful to develop new treatment approaches targeting mechanisms of AUD with the goal to reduce relapse rates after discharge from the hospital.

Regarding the second modality, recently, novel approaches that integrate mental training practices (i.e., MBIs) with wearable brain-sensing NF devices online showed their improved potential for the improvement of cognitive skills needed for promoting efficient stress management (Balconi et al., 2017b, 2019b; Bhayee et al., 2016; Crivelli et al., 2019b). In particular, Balconi et al. (2017b) examined the conscious and unconscious mechanisms of MBIs supported by an NF wearable device, in emotion regulation and stress management. They showed how MBI can be suitable in regulating affective responses to external stimuli and stressful events, enhancing the ability to handle implicit negative emotions.

The training procedure consists of 4 weeks of mental practice based on a mindfulness approach supported by dedicated brain-sensing wearable devices—namely the Muse™ headband (InteraXon Inc., Ontario, Canada) or the Lowdown Focus glasses (Smith Optics Inc., Clearfield, UT). The devices embed dry EEG electrodes, which allow non-invasive recording of neural activity from the frontal and posterior regions of the brain. A dedicated smartphone app then uses such electrophysiological data to immerse the practitioners in an interactive sound environment able to provide a real-time feedback on his/her level of focusing vs. distraction, based on related EEG markers.

Such a wearable neurofeedback system was specifically devised to support meditation practice and inform practitioners on their mindset by modulating natural sounds. Adaptive feedback provided them information on mind-wandering and then prompted their non-judgemental acceptance of such phenomenon and their intentional return to breathing sensations.

The protocol includes pre-/post-training assessment based on psychometric, neuropsychological and cognitive performance measures, as well as detection of neurometric and autonomic markers of neurocognitive efficiency and adaptive stress

management. Findings so far suggested the potential of the intervention in enhancing attention regulation at the neurophysiological level, EFs' emotion regulation, fostering efficient psychophysiological reactivity and homeostatic mechanisms regarding the stress response. Further, it hints at its potential for promoting both better subjective experience and objective markers of the stress response by strengthening central neural regulatory skills and awareness of EEG signatures of distraction and dysfunctional hyperactivation (Balconi et al., 2019b).

The training protocol has been validated by previous research in both experimental and applied contexts, with different samples, athletes, professional managers, car drivers, elderly and young adults (Balconi et al., 2020, 2019a; Crivelli et al., 2019a, c).

Possible development of this approach proven to be effective with multiple samples will be the application of MBI + NF wearable device as an add-on intervention in SUD and BA, for targeting especially EFs' enhancement.

6.5 Conclusions

To summarize, in this chapter, MBIs have been described considering their application to addiction-related disorders, SUD as well as BAs. Special attention has been given to the therapeutic mechanisms of MBIs as a treatment for addiction and on the neurocognitive correlates on which MBIs impact.

In general, understanding the neurocognitive mechanism underlying a type of treatment is not necessary to establish whether a given treatment modality is an empirically supported intervention; however, deepening the underlying basis of the link between mindfulness and neural correlates in addiction can inform the refinement of MBIs to produce larger clinical effects and additional long-term therapeutic benefits.

Therefore, the neurophysiological evidence of the effects of MBIs' application on EFs mainly in SUD has been reported in several points of the discussion. An emerging body of research suggests that MBIs have so far proved effective in reducing craving, reward sensitivity, stress reactivity and negative affect on a general level in SUD; while for EFs, MBIs may act on the deautomatization of addictive responses, decision-making, reaction inhibition, self-control and attention regulation.

Some of these neurophysiological results were mainly observed in individuals with addiction to tobacco, alcohol and opioids, while to date, there seems to be scarce literature on the neurophysiological effects of MBIs in other populations with both substance and BAs. Generally, research is still more focused on the clinical outcomes (e.g., reduction of symptoms severity, relapse) than on the specific effects that can be grasped at the neurophysiological level or/and on the EFs.

The reason and our interest for focusing on neurocognitive correlates of the intervention are that they constitute the target neurophysiological basis for protocols that combine neuroscientific tools with MBIs for boosting EFs in addiction-related

disorders. In fact, the last paragraphs of this chapter discussed the proposal of combining the application of MBIs supported by neurofeedback devices, describing how to promote behavioural self-regulation through the self-regulation of cortical activity. The training MBI + NF protocol described here has been validated by previous research in both experimental and applied contexts and showed promising results whose extension deserves to be tested in addicted populations.

Therefore, to the future research agenda inherited from the studies of Garland and Howard (2018) and Garland et al. (2019) highlighting some of the future steps needed (such as the sequencing of MBIs in multimodal care packages; the need to understand dose–response relationships; testing research rigour and reproducibility; treatment optimization based on neuroscientific discoveries; standard treatment formats), we add the proposal of testing the combination of MBIs and NIBS, to synergistically impact on bottom-up and top-down cognitive processes, as an approach with potentially interesting long-term clinical outcomes.

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Chapter 7
Neuromodulation Techniques in the Treatment of Addictions

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7.1 Introduction

Firmly grounded in a vision that addiction is a brain disease (Leshner, 1997), neurostimulation emerged as an encouraging set of techniques aimed at restoring brain functions and improving clinical trajectories (Ekhtiari et al., 2019). It capitalised on influential theories that considered abnormal neurocognitive functioning as a key dimension of addiction (Goldstein & Volkow, 2002, 2011; Koob & Volkow, 2016; Noël et al., 2013; Robbins & Everitt, 1996; Robinson & Berridge, 2008, 2016).

Indeed, the progress made in brain imaging over the last decades represents a marked advancement in our understanding of substance use disorder (SUD) (American Psychiatric Association, 2013), as it offers concrete and effective modelling of addictive states' neurobiological underpinnings (Parvaz et al., 2011). While the initial investigations mainly focused on limbic-dysregulated activity and the reward system, the research emphasises a wider disrupted neuronal circuitry of addiction (Goldstein & Volkow, 2011; Noël et al., 2013; Koob & Volkow, 2016). Indeed, SUD could arise from an imbalance between three separate but interacting neural systems: a reflective, principally prefrontal cortex (PFC)-dependent system involving inhibitory control and decision-making, predicting the future consequences of behaviour; an impulsive system, mostly on the amygdala-striatum, promoting automatic, salient and habitual behaviours; and the insula that integrates

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interoception, which further integrates conscious feelings and decision-making processes involved in short risky profit (Noël et al., 2013).

In addition to pharmacological intervention (Mann et al., 2014), a growing amount of data has promoted the efficacy of non-pharmacological neurocognitive interventions for SUD (Coles et al., 2018; Noël et al., 2019). To date, the dorsolateral prefrontal cortex (DLPFC) has been the most targeted brain area for improving cognitive control, decision-making and reducing craving intensity (Bechara, 2005; Lüscher et al., 2020; Zilverstand et al., 2018). Insula has recently become a highly relevant subject for reducing SUD symptoms (Ibrahim et al., 2019).

In this chapter, we briefly summarise key findings on the following: (1) deep brain stimulation (DBS), an invasive and focal electrical therapy using electrodes implanted deep into the brain; (2) repetitive transcranial magnetic stimulation (rTMS), a non-invasive technique using a stimulation coil over the scalp delivering a magnetic pulse through the skull over a period; (3) transcranial direct current stimulation (tDCS), a painless non-invasive device delivering low direct current across the scalp with a positive (anodal) and a negative (cathodal) electrode; and (4) neurofeedback (NF), a brain–computer interface using a real-time display of brain activity fed back to the patient so they can learn to implement strategies to regulate their brain activity.

7.2 Invasive Brain Stimulation

DBS is an invasive technique that continuously stimulates brain areas in the long term (Herrington et al., 2016; Montgomery & Gale, 2008). It consists of a pulse generator implanted with brain surgery, with four electrodes placed in deep brain areas. It is possible to turn the system off/on or modify its frequency and intensity. In the 1980s, DBS was applied as an intervention for movement disorders and treating tremors in patients with Parkinson's disease (Benabid et al., 1987). During the 2000s, it was used in psychiatric disorders for patients with treatment-refractory disorders, first in obsessive-compulsive disorder (Nuttin et al., 1999), followed by major depression (Mayberg et al., 2005). Case studies observing the effect of DBS on the nucleus accumbens (NAc) in patients with Parkinson's disease and psychiatric patients with concomitant alcohol and nicotine use disorders show an unexpected reduction in consumption (Ardouin et al., 2006; Kuhn et al., 2007, 2009). Following these observations, Luigjes et al. (2012) suggested stimulating the NAc, involved in motivation and inhibitory control.

Eight case studies have explored the effect of DBS on addiction among a total of 11 patients (meta-analysis Luigjes et al., 2019). Four focused on alcohol use disorder (Voges et al., 2006; Müller et al., 2009, 2016; Kuhn et al., 2011), three on opioid use disorder (Zhou et al., 2011; Valencia-Alfonso et al., 2012; Kuhn et al., 2014) targeting the bilateral NAc and one on cocaine use disorder focusing on the bilateral anterior cingulate cortex (Gonçalves-Ferreira et al., 2016). Most patients were still abstainers after at least 12 months. All opioid use disorder patients and half alcohol

disorder patients were abstainers, while half alcohol use disorder patients and all cocaine use disorder patients were non-abstainers with reduced consumption. A study comparing methadone maintenance and DBS as a treatment for opioid use disorder showed that over 6 months, 47% of patients under methadone had opiate-free urine against 49% on DBS (Stephen et al., 2012).

The results were positive for addiction disorders, but the problem is that DBS is extremely invasive, with 0.4% surgeries leading to death and 2% leading to adverse events (e.g., haemorrhage problems) (Voges et al., 2006). Although DBS appears to be well tolerated after recovery from brain surgery, the risk seems too high and knowledge too unclear to suggest it as common clinical practice for addiction treatment (Carter & Hall, 2011). Indeed, the mechanisms underlying the beneficial effects of DBS have been investigated (Luigjes et al., 2012, 2019; Pierce & Vassoler, 2013; Herrington et al., 2016). The identified mechanisms include neuroplasticity and possibly neuroprotection and neurogenesis (Jakobs et al., 2019) for exhaustive cellular mechanisms.

In conclusion, studies on DBS have yielded positive clinical outcomes, but the cost–benefit ratio is questionable and ethically disputable. DBS should be reserved for patients refractory to any other less invasive treatment as a last resort.

7.3 Non-invasive Brain Stimulation

Strengthening the brain area for clinical improvement without brain surgery and fatal risk was the main aim of non-invasive brain stimulation (NIBS). Although NIBS are less powerful, they allow interventions with fewer risks and adverse events (Rossi et al., 2009, 2020). The first recommendations for using NIBS for clinical purposes date back to 1994 (Rossini et al., 1994). Since then, numerous clinical trials have been conducted in psychiatry (Tortella, 2015; Kekic et al., 2016; Lefaucheur et al., 2017; Fregni et al., 2020), including SUD (Jansen et al., 2013; Grall-Bronnec et al., 2014; Hone-Blanchet et al., 2015; Schluter et al., 2018; Ekhtiari et al., 2019; Luigjes et al., 2019; Stein et al., 2019; Song et al., 2019; Bollen et al., 2021). The most studied NIBS are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS is less invasive than DBS but more invasive than tDCS. rTMS can induce action potential by magnetic stimulation. tDCS, using electric stimulation, is easier and cheaper than rTMS. Multiple sessions of NIBS are safe even for children and adolescents with a similar rate of adverse events as adults, which are mainly headache (11.5%) for rTMS and redness (4.7%), itching (5.8%) and tingling (11.5%) for tDCS (Krishnan et al., 2015).

Both techniques are recommended to be repeated for at least five 5- to 30-min sessions over the DLPFC to be effective in SUD (Luigjes et al., 2019; Song et al., 2019). In SUD patients, DLPFC activation is disrupted, reflecting poor memory, attention and inhibitory capacity in the context of substance-related stimuli (Goldstein & Volkow, 2011). Indeed, the DLPFC is involved in inhibitory control

and decision-making, resisting the urge (Bechara, 2005; Koechlin & Hyafil, 2007; Badre & Nee, 2018; Zilverstand et al., 2018). Induced craving is linked to DLPFC in eight functional magnetic resonance imaging (fMRI) studies (Wilson et al., 2004). It correlates with glutamatergic dysfunction in the NAc and the anterior cingulate cortex, which are two important areas of the reward system (Bauer et al., 2013). An imbalance between the hyperactive emotional system and the hypoactive executive function system is hypothesised to reflect the chronicity of addiction disorders (McClure & Bickel, 2014; Zilverstand et al., 2018; Lindgren et al., 2019). The DLPFC is the most relevant area to be strengthened via the NIBS (Lapenta et al., 2014; Sauvaget et al., 2015; Baeken et al., 2016; Lefaucheur et al., 2017; Luigjes et al., 2019; Song et al., 2019; Fregni et al., 2020; Bollen et al., 2021).

A meta-analysis of 48 NIBS studies concluded that DLPFC neuromodulation has a small effect on craving and a moderate effect on consumption, with no significant difference between the type of substance (alcohol, illicit drugs, nicotine or eating disorders), neuromodulation (rTMS or tDCS) or DLPFC stimulation laterality (left or right DLPFC). Several repeated sessions were more effective than a single session. Moreover, craving and the total sessions showed a positive linear association (Song et al., 2019).

7.3.1 Repetitive Transcranial Magnetic Stimulation

The rTMS uses a coil placed on the scalp stimulating magnetic pulses through the skull in intervals. The magnetic field involves a focal electrical current that depolarises underlying cortical neurons. The frequency, intensity and duration of current, with the properties and area, influenced the effect. The rTMS can be either low frequency (<2 Hz) to inhibit the target area and decrease its activity or high frequency (>5 Hz), also called deep TMS, to increase the regulating activity and excite the target area (Chen et al., 1997; Siebner et al., 2000; Luigjes et al., 2019).

Typically, for addictive disorders' studies, rTMS targets the right DLPFC with a high frequency to excite the area (Amiaz et al., 2009) or the left DLPFC at a low frequency to inhibit it (Trojak et al., 2015). A recent meta-analysis based on 26 studies found that rTMS over the left DLPFC reduces craving and the bilateral DLPFC reduces consumption, compared to sham stimulation (medium and robust effect) (Zhang et al., 2019a). The DLPFC seems to be the most accurate area to target, but laterality remains a controversial issue. Song et al. (2019) did not find a difference between the right and left hemisphere, while Maiti et al. (2017) found an effect on nicotine craving with rTMS on the bilateral DLPFC. Enokibara et al. (2016) also found a craving reduction with rTMS on the right DLPFC. This controversy could be due to the small number of clinical trials, small sample sizes and high heterogeneity (e.g., type of SUD, baseline characteristics of the sample, rTMS method, number of sessions and context such as psychiatric and pharmacologic interventions). Although the rTMS effect did not significantly differ by the SUD type, the craving effect size was small for alcohol use disorder, medium for nicotine

use disorder and large for illicit drugs. Additionally, more pulses during stimulation were associated with a greater craving effect size (Zhang et al., 2019a).

Five 8-min sessions of 10 Hz rTMS over the left DLPFC reduced the craving of methamphetamine use disorder patients compared to sham (Su et al., 2017). The blinding TMS procedure commonly uses a sham coil without an electromagnetic pulse or a considerably low current to imitate the cutaneous sensation on the scalp muscles (Ekhtiari et al., 2019). Many clinical trials do not include sham rTMS conditions for comparison but use controlled conditions such as waiting lists or habitual rehabilitation (e.g., Liu et al., 2020). A recent clinical trial showed that 20 sessions of 10 Hz rTMS with rehabilitating female methamphetamine use disorder patients reduced their craving for at least 30 days after discharge compared with the control group (Liu et al., 2019). Young female patients showed a greater craving reduction, possibly due to greater cortical plasticity. Additionally, rTMS was more effective in the high-craving subgroup. Indeed, induced craving to activate its neuronal network could make the intervention more effective. A recent randomised, double-blinded, sham-controlled trial showed that rTMS (10 sessions over 2 weeks at 10 Hz, 300 pulses per session) over the left DLPFC along with a smoking video allowed smokers to reduce not only craving cues but also cigarette consumption during the 2-week treatment and 1 month after the treatment (Li et al., 2020).

In addition, other potential target areas could be the insula and medial PFC, which are involved in the maladaptive response in a stressful or rewarding context, influencing decision-making (Euston et al., 2012). After brain damage in the insula, patients are likely to stop smoking easily and not feel a craving after quitting (Naqvi et al., 2007). It corroborates the involvement of the insula in craving (Bonson, 2002) and decision-making (Naqvi & Bechara, 2010). These findings suggest that the insula is a potential target for neuromodulation (Ibrahim et al., 2019). To date, the first and only SUD clinical trial targeting this area was a double-blinded, randomised study using bilateral stimulation over the DLPFC and insula (Dinur-Klein et al., 2014). In total, 115 smokers intending to stop smoking received 13 sessions of either high-frequency rTMS (10 Hz), low-frequency rTMS (1 Hz) or sham rTMS, with or without presentation of smoking cues (six subgroups in total; condition 3 × 2). High-frequency rTMS significantly reduced the number of cigarettes consumed, the Fargerström Test for Nicotine Dependence (evaluating the dependence), and increased the abstinence rate compared to low-frequency rTMS and sham rTMS, especially when applied with smoking cue exposure. High-frequency rTMS showed a reduction in cigarette consumption at 6-month follow-up compared to sham rTMS but not compared to low-frequency rTMS or the condition without exposure. Insula stimulation with deep rTMS is promising for reducing cigarette consumption in the long term.

The newer forms of rTMS have also yielded encouraging results, such as intermittent theta-burst stimulation (iTBS), which is a shorter intervention than typical rTMS (approximately 5 min against 8–10 min) (Chen et al., 2020b; Su et al., 2020). A clinical trial on methamphetamine use disorder patients showed that 20 daily sessions of iTBS over the DLPFC (900 pulses per day) reduced craving and improved cognition and sleep quality compared to sham conditions (Su et al., 2020).

7.3.2 Transcranial Direct Current Stimulation

The tDCS is the most investigated neuromodulation among transcranial electrical stimulation (tES) classification. The tES is a classification of non-invasive stimulation intended to change brain activity by passing an electrical current. Depending on the technique, there are several tESs (Bikson et al., 2019): transcranial random noise stimulation (tRNS) uses a random stimulus to desynchronise pathological rhythms (Terney et al., 2008); transcranial pulsed current stimulation (tPCS) uses either monophasic or biphasic pulsed waveforms (Jaberzadeh et al., 2014) and transcranial alternating current stimulation (tACS) uses a sinusoidal current waveform (Antal et al., 2008). For blinding, studies used sham tES, a short duration stimulation (10–30 s) to give the cutaneous sensation of being stimulated (Ekhtiari et al., 2019).

tDCS is electric neuromodulation that acts with a low intensity of constant current applied by two electrodes on the scalp. The current may vary between 0.5 and 2 mA and last between 10 and 40 min with fade in and fade out (10–30 s) of the current (Higgins & George, 2019). tDCS can be used in three montages (Zhao et al., 2017). The bi-cephalic montage indicates that the anode and cathode are placed on the scalp, the anode delivers current to the brain and increases cortical excitability, and the cathode inhibits brain excitability and current escapes from it (Nitsche & Paulus, 2000, 2001). The distance between the two electrodes on the scalp can influence the strength of neurostimulation (Bikson et al., 2010). In the mono-cephalic montage, the anode is placed on the scalp and the cathode on the body as the reference electrode (e.g., arm or neck). It makes possible to focus on the observation of the anode effect and limit confusion. The non-cephalic montage suggests non-cortical stimulation, such as the cerebellum (Zhao et al., 2017).

Similar to other NIBS, the mechanisms of tDCS are still unclear (Nitsche et al., 2003; Arul-Anandam & Loo, 2009; Stagg & Nitsche, 2011; Brunoni et al., 2012; Philip et al., 2017; Zhao et al., 2017). The literature suggests that tDCS mechanisms act like long-term potentiation and long-term depression (Nitsche et al., 2003). The action potentials are modulated by tDCS even after the stimulation period (Nitsche & Paulus, 2000, 2001), and several neuromodulation sessions could increase the duration of the effects (Boggio et al., 2007). The mechanisms of tDCS during and after stimulation are different. During stimulation, anodal and cathodal tDCS modulates neuronal excitability by altering the resting membrane potential of neurons. The modulation persists after stimulation and produces glutamatergic and GABAergic synaptic plasticity as an aftereffect (Stagg & Nitsche, 2011). Contrary to TMS, tDCS itself is not sufficiently high to directly cause neuronal firing. If the intrinsic fluctuation of the neuron voltage is close to the threshold, the tDCS excitation can make it a potential action (Philip et al., 2017). Therefore, tDCS responsivity depends on cortical excitability, influenced by age, gender, anxiety level, lack of sleep, hormonal status and medication (Sauvaget et al., 2015). There are significant inter-individual differences in response to tDCS (Strube et al., 2016), contextual or inherent (Fertonani & Miniussi, 2017; Li et al., 2015).

Although this neuromodulation has been investigated as an intervention in SUDs (Hone-Blanchet et al., 2015; Schluter et al., 2018; Luigjes et al., 2019; Chen et al., 2020a), not so much for behavioural addiction, the data have been encouraging (Sauvaget et al., 2015). The new guidelines of Fregni et al. (2020) categorised tDCS as an effective treatment for reducing craving and relapse in addictive disorders, especially in alcohol use disorder. The recommendation is bilateral stimulation with the right DLFC anodal and the left DLPFC cathodal tDCS (F4 and F3 positions, respectively, according to the 10–20 international system for electroencephalography [EEG] electrode placement). More tDCS studies are required to conclude regarding crack-cocaine or methamphetamine use disorders. A longer duration of stimulation is related to a larger effect size in reducing craving (Chen et al., 2020a). Multiple sessions improve craving reduction compared to a single tDCS session (Song et al., 2019; Chen et al., 2020a).

A recent clinical trial showed that 10 sessions of DLPFC tDCS over 5 weeks on methamphetamine use disorder patients reduced craving and improved executive functions immediately after and 1 month after the intervention. Interestingly, there is a significant correlation between the reduction in craving and cognitive control improvement (Alizadehgoradel et al., 2020). Most clinical trials have targeted craving. Numerous meta-analyses have reported a reduction in craving (Jansen et al., 2013; Sauvaget et al., 2015; Lupi et al., 2017; Spagnolo & Goldman, 2017; Chen et al., 2020a, b; Kang et al., 2019; Luigjes et al., 2019; Song et al., 2019; Bollen et al., 2021). A recent meta-analysis of 32 tDCS studies found a medium effect in reducing craving, indicating more effect with longer stimulation sessions and a higher number of sessions (Chen et al., 2020a).

Few clinical trials have investigated the effect of tDCS on the relapse rate. At the 6-month follow-up after 10 sessions of tDCS, eight patients suffering from alcohol use disorder were still abstainers in the active condition against two in the sham condition (50% vs. 11.8%) (Klauss et al., 2014). The DLPFC stimulation can increase the quality of life and can decrease the relapse rate in patients suffering from alcohol use disorder, sometimes without reduced craving, depressive and anxiety symptoms, or improved cognitive function (13 min × 10 sessions twice a day of 2 mA stimulation, anode-right and cathode-left DLPFC, and 6-month follow-up) (Klauss et al., 2014) and sometimes with reduced craving (20 min × 10 daily sessions of 2 mA stimulation, anode-right and cathode-left DLPFC, and 3-month follow-up) (Klauss et al., 2018b). In the same design as in Klauss et al. (2018b) but on patients with crack-cocaine use disorder (Klauss et al., 2018a), the relapse rate was not affected. Another clinical trial with guided tDCS (10 sessions of 2 mA, anodal-right DLPFC and cathodal-left DLPFC over 5 consecutive days) did not reduce the craving or relapse rate or improve cognitive function in patients with cocaine use disorder (Verveer et al., 2020). Nevertheless, active tDCS reduced the relapse rate in the crack-cocaine subgroup users compared to sham tDCS.

Despite the positive impact of tDCS on craving and relapse rate, results remain inconsistent across clinical trials. This is possibly due to the large heterogeneity of the experimental setting (e.g., type of substances, targeted area, localisation of anode/cathode, ampere of tDCS, duration of stimulation, the time between sessions,

number of sessions) (Luigjes et al., 2019; Chen et al., 2020a) and variations between the studied samples (e.g., characteristics of the sample at baseline, sample size, study design) (Bollen et al., 2021). Although most studies use a between-subjects design comparing multiple conditions (e.g., active tDCS vs. sham), a within-subjects design (e.g., a sample performing both conditions in a counterbalanced order) could limit baseline bias. Further, cognitive remediation during tDCS could improve cognitive functions and reduce clinical symptoms (Elmasry et al., 2015; Dedoncker et al., 2016; Noël et al., 2019; Zhang et al., 2019b; Bollen et al., 2021).

7.3.3 Combined Non-invasive Brain Stimulation

NIBS techniques have the advantage of being combined with other interventions. In most cases, the participant is passively stimulated (i.e., in the absence of any effort), while in other cases, another intervention may be offered simultaneously (e.g., cognitive remediation, rehabilitation of cognitive biases, mindfulness or psychotherapy, simultaneously with tDCS). Combining complementary interventions could (1) combine the effects of the two interventions and (2) potentiate the effects through synergy (Dedoncker et al., 2021).

tDCS can be especially suitable for combined intervention because the sensation is minor and should not distract the patient during a task. According to the activity-selectivity assumption, tDCS preferentially induces modulation in already activated neuronal networks compared to inactive neuronal networks (Bikson et al., 2013). Therefore, it seems possible to target specific neuronal networks by inducing neuronal pre-activation with cognitive training or substance-related stimuli. For the synergistic effect on neuronal plasticity change, tDCS and cognitive training or psychotherapy should activate the same neuronal pathway (Dedoncker et al., 2021).

The combination of these therapeutic interventions, such as exogenous neuromodulation (e.g., tDCS) and endogenous activation (e.g., cognitive training or psychotherapy), has been investigated in a few studies with non-clinical participants and participants with cognitive impairments (Elmasry et al., 2015; Zhang et al., 2019b). To date, no clinical trial in SUD has combined tDCS with psychotherapy. However, eight have combined tDCS with cognitive training related to SUD. Two randomised controlled clinical trials in alcohol use disorder combined tDCS with cognitive bias modification (CBM) (den Uyl et al., 2017, 2018).

CBM is a broad classification of cognitive training focused on cognitive bias retraining. It uses images related to a specific SUD substance that needs treatment. The alcohol attentional bias modification (ABM) uses a dot-probe task to exercise visual disengagement from alcohol images by associating alcohol-related images on the opposite side of the dot to be viewed. It may also use the alcohol approach-avoidance task (AAT) to train the subject to push away the alcohol-related images with a joystick to create an avoidance tendency towards alcohol (developed by Wiers et al., 2009). Four alcohol AAT sessions during 1 week of hospitalisation for alcohol use disorder reduced the abstinence rate by 17% 2 weeks after discharge

(Manning et al., 2021). Meta-analyses of CBM show a reduced relapse rate (Allom et al., 2016; Jones et al., 2016), cognitive biases and cue reactivity (Boffo et al., 2019; Loijen et al., 2020). However, their effects are still limited. Cognitive training could be an interesting add-on treatment for addictive disorders, at least in the short term (Manning et al., 2021).

Two studies combined tDCS with CBM during hospitalisation for inpatients with alcohol use disorder inpatients (den Uyl et al., 2017, 2018). They did not follow the recent guidelines (Fregni et al., 2020) but proposed 20-min neuromodulation at 2 mA with anodal tDCS over the left DLPFC (35 cm^2) and cathodal tDCS over the right DLPFC (100 cm^2) (den Uyl et al., 2017). The two studies differed in the type of CMB. The first retrained the AAT with a joystick (push 90% of alcohol images and 10% of soft drink images; pull 90% of soft drink images and 10% of alcohol images in the active training task; 50% of pull and push in the inactive training task) (den Uyl et al., 2017). The second was the alcohol ABM via a dot-probe task with two stimuli: either alcohol or soft drink images or, in some cases, two soft drink images (absent target or two objects as a surprise trial). In the active training, the contingency probe after alcohol was 90% and 10% after alcohol stimuli (50/50 in the inactive version) (den Uyl et al., 2018). The first study investigated the potential effects of four stimulation sessions on the DLPFC simultaneously with alcohol approach tendency retraining (4× tDCS + AAT, three groups in parallel design) on alcohol bias, craving and relapse after 3 months and 1 year post-discharge (den Uyl et al., 2017). The second study investigated the effects of four sessions of simultaneous simulation on DLPFC combined with ABM (4× tDCS + ABM, 2 × 2 factor parallel design) on craving, alcohol bias and relapse after 1 year (den Uyl et al., 2018). One year after hospitalisation with the combined intervention, den Uyl et al. (2018) showed non-significant results for alcohol relapse rate. Nonetheless, the relapse rate trend was in the expected direction: the combined condition (21%), followed by active tDCS with inactive ABM condition (31%), sham tDCS with active ABM condition (38%) and a worse relapse rate in sham tDCS with inactive ABM condition (45%). A trend-level effect appeared for the first study showing that tDCS concurrent with active training reduces the relapse rate at 1 year only compared to sham tDCS (no difference compared to tDCS separated to the CBM) (den Uyl et al., 2017). Notably, the trend effect appears only when they consider other predictors (gender, duration of alcohol problem, number of detoxifications, alcohol problems, duration of treatment, depression symptoms and scored craving) in the logistic regression. Moreover, there was no effect at the 3-month follow-up.

There are no significant results showing the interest in combining tDCS with CBM. Nonetheless, the two studies measured only long-term relapse (3-month and 1-year follow-up), and results went in the expected direction, showing an average lower relapse rate in the active tDCS condition simultaneous with CBM at 1-year follow-up (den Uyl et al., 2017, 2018). The combined intervention did not influence alcohol-scored craving. However, it was extremely low in patients. Perhaps induced craving is a more sensible measure, as den Uyl et al. (2016) found that active combined tDCS reduces the induced craving (by alcohol images) in EEG tasks in heavy drinkers. More combined clinical trials following the tDCS guidelines

(anode-right DLPFC and cathode-left DLPFC and >5 sessions) (Noël et al., 2019) and measuring early relapse should be investigated (Manning et al., 2021). In addition, reducing the electrode surface could increase the effect (Bollen et al., 2021).

The learning effect of tDCS can be observed 'online' (i.e., during the training with the tDCS) or 'offline' (i.e., the same task after the intervention). With online learning data, it is possible to see if the stimulation increases the learning effect of the cognitive task by comparing the improvement in training in the active tDCS condition compared to the sham tDCS condition. The two studies on AUD patients by den Uyl et al. (2017, 2018) revealed in exploratory analyses that the learning process has been improved by active tDCS on the DLPFC. The first study showed a learning effect on the approach alcohol bias enhanced by tDCS between sessions 1 and 2; however, it disappeared in the last two sessions (mini-assessment before each of the four interventions) (den Uyl et al., 2017). The second study also found an enhancer effect of tDCS on the ABM. The combined intervention with active tDCS and active ABM had a stronger avoidance bias (only with the analysis of the mean of the four sessions) (den Uyl et al., 2018). In conclusion, although the results are fragile, they suggest that tDCS could accelerate the learning process of CBM with ABM and AAT. However, they failed to maintain the effect on offline measures with a similar task after treatment.

To our knowledge, only one clinical trial combining rTMS with another intervention has been reported (Trojak et al., 2015). It combined 10 sessions of low-frequency rTMS with nicotine replacement therapy (nicotine in the form of gum). It showed an improvement in cigarette abstinence directly after the 2-week intervention, but the effect did not last. As there are only two groups comparing sham and verum rTMS, it is impossible to determine if the effect is from this combination. To date, concurrently combining rTMS with CBM or cognitive training has not yet been studied in SUD. Muscular and cutaneous sensations induced by rTMS could not allow the patient to focus correctly on the other intervention. Thus, sequential complementary interventions would be more appropriate.

In conclusion, few studies have combined NIBS concurrently with a complementary intervention, and they did not follow the new recommendations. Further studies combining more than four sessions of bilateral tDCS with anode-right DLPFC and cathode-left DLPFC simultaneously with CBM, cognitive revalidation or psychotherapy are encouraged. Studies combining insula high-frequency rTMS or DLPFC high/low-frequency rTMS during sequential CBM, cognitive revalidation or psychotherapy will advance clinical research.

7.4 Neurofeedback

From Richard Caton's first description of brain electrical activity (1875) to our actual knowledge of EEG, a history of neurophysiology has led to breakthrough advances in technology, allowing an in-depth assessment of brain functioning and

neuromodulatory interventions. In 1935, after Berger (1929) discovered the now vastly recognised synchronised 'alpha EEG rhythm', Alfred Lee Loomis demonstrated that conditioning could be applied to EEG activity by bringing alpha rhythm under voluntary control. This period marked the first demonstration of EEG biofeedback. Subsequently, during the 1960s, Maurice (Barry) Sterman became a pioneer of EEG-biofeedback clinical application through his work on internal inhibition and basal forebrain modulation together with Carmine Clemente at UCLA (USA) (Arns & Sterman, 2019). Currently, there is a definite and growing interest, in both clinical and research domains, towards this neuromodulation technique evidenced by its application to a large sample of psychiatric ailments such as addiction (Cox et al., 2016; Dousset et al., 2020; Horrell et al., 2010), posttraumatic stress disorder (Reiter et al., 2016) and schizophrenia (Balconi & Vanutelli, 2019; Rieger et al., 2018). It has even extended to enhancing healthy subjects' abilities, such as improving performance (Arns et al., 2008; Crivelli et al., 2019).

Essentially, biofeedback is the use of instrumentation to mirror psychophysiological processes of which the individual is not normally aware, and which may be brought under voluntary control (Thompson & Thompson, 2015). In that respect, neurofeedback (NF) stands for a specific kind of biofeedback, with reflected information being cerebral activity measurements. Interestingly, biofeedback is a natural and universally shared regulatory mechanism as our biological system evolves by constantly adapting itself according to the information sent by the peripheral nervous system, just as NF displays are sent by the optic or auditory pathways (Thompson & Thompson, 2015). In this subsection, we will expose the theoretical and methodological aspects of NF, its application through fMRI and EEG interfaces, and the future perspectives towards a better practice.

7.4.1 Theoretical and Methodological Aspects

From a methodological perspective, brain activity measures are converted into visual or auditory signals fed back in real-time to the patient. The patient is asked to work on this fed-back display via mental strategies such as imagining particular events happening (e.g., moving a limb of the body, thinking about negative consequences of drug consumption, etc.), and expected changes are positively reinforced (Cox et al., 2016). Consequently, patients control their responses, see their progress in real-time and achieve optimum performance to control their symptoms or an unwished behaviour (Cox et al., 2016). Thus, NF requires patients to take on an active role in their care—finding personal mental strategies impacting brain activity by themselves and actively implementing them repetitively. Therefore, contrary to medication or compared to the aforementioned neuromodulation techniques (TMS and tDCS) that imply passive involvement, as learning is an active process requiring repetition of training sessions, NF entails implication, motivation and dynamic engagement from the patient.

Theoretically, by rewarding successive approximations, we can shape a behaviour: The patient learns to switch on or switch off a specific network in the brain, and if it is often enough, neuroplastic changes will occur, based on learning (Thompson & Thompson, 2015). Indeed, '… brain plasticity can be induced by demands associated with training, practice or learning and is defined as the brain capacity to continuously remodeling the neuronal synaptic organization in order to optimize the brain's networks functioning …' (Kubben, 2012). To a large degree, this learning process relies on operant conditioning and the fundamental principle of Thorndike's law of effect, whereby rewarding behaviour increases the likelihood of its recurrence (Sterman, 1996; Thompson & Thompson, 2015). In operant conditioning of brain waves, the patient receives a reward (e.g., a smiley or a sun, indicating the level of the current performance) when they successfully put themselves in the targeted mental state—a process that will become almost automatic after several practice sessions. Subsequently, as patients face salient stimuli leading to an intense and irrepressible desire of the substance and ultimately result in consumption, the last step is to apply the learned skill in ecological situations, a transfer process hypothesised to involve classical conditioning (Thompson & Thompson, 2015).

Thus, NF offers the possibility to modify cortical activity, a phenomenon that cannot be achieved without objective brain measurements (Micoulaud-Franchi et al., 2013; Thibault et al., 2016). There are several interfaces for the application of NF, including EEG, fMRI, functional near-infrared spectroscopy (fNIRS) and magnetoencephalography (MEG), many of which involve different technologies and, thus, different procedures (Alkoby et al., 2018; Orndorff-Plunkett et al., 2017; Thibault et al., 2016). Currently, the widespread forms mostly involve fMRI-NF and EEG-NF (Dickerson, 2018). Applied to NF, each method presents its advantages and drawbacks (Thibault et al., 2016; Orndorff-Plunkett et al., 2017). However, a common interesting feature is that it allows targeting neural networks and is not limited to the intervention on just one brain region. Addictive disorders are characterised by abnormal behaviours generated by dysfunctional neurocognitive networks (Kalivas & Volkow, 2005; Noël et al., 2013). By modulating these networks, NF investigation seems to be attractive and promising for reducing symptoms and promoting resilience in favour of an optimal intercession (Sitaram et al., 2017).

7.4.2 Functional Magnetic Resonance Imaging Neurofeedback

As the fMRI-NF offers a good spatial resolution, it has the advantage of localising brain signals to specific areas (Cox et al., 2016). Once the regions of interest (ROIs) have been identified through the peak of the BOLD signal, an NF-training protocol can be implemented to modulate (increase or reduce) neural activity in these particular ROIs (Bracht et al., 2021; Hanlon et al., 2013). Many studies have

demonstrated the effectiveness of fMRI-NF training protocols in patients suffering from addiction by manipulating relevant brain regions related to the abnormal bottom-up system that generates a 'wanting' (craving) behaviour (Luigjes et al., 2013). In fact, it appears that NF training impacts abstinence by reducing the activity of craving-related regions—the anterior cingulate cortex (ACC) (Hartwell et al., 2016; Karch et al., 2019), PFC (Hartwell et al., 2016; Karch et al., 2019), insula and ventral striatum (Kirsch et al., 2016)—and the feedback on the connectivity between the anterior (frontal) and posterior regions (temporal and parietal) (Karch et al., 2019; Luigjes et al., 2019). Conjointly, ACC activity correlates with craving ratings, and patients might be more able to exert voluntary control over the ACC than the PFC (Fovet et al., 2015; Hanlon et al., 2013; Hartwell et al., 2016; Li et al., 2013). Notably, these areas are mostly included in the reward system, which plays a major role in adaptive behaviour, control of behaviours and learning processes (Bari et al., 2018; Karch et al., 2019). Some studies have already attempted to identify the network involved in the brain self-regulation process during real-time fMRI-NF training. This network mostly recruits the anterior insular cortex, basal ganglia and ACC. These regions are recurring targets of fMRI-NF protocols. Therefore, NF studies face a new challenge by considering the potential overlap between the activated regions in response to the NF-induced regulatory phenomenon and the regions whose activity constitutes the target of the experimental protocol for symptom reduction (Emmert et al., 2016).

7.4.3 Electroencephalography Neurofeedback

As NF relies on real-time processes, EEG-NF presents a clear advantage for optimal learning owing to its high temporal resolution (Dousset et al., 2020). EEG-NF is used as a neuromodulation technique to identify target brain frequencies, to increase or reduce specific forms of EEG activity (Gunkelman & Johnstone, 2005). Thus, EEG-NF protocols rely on electrical activity recorded from the scalp and mainly focus on alpha (8–12 Hz), beta (13–30 Hz), delta (0–4 Hz), theta (4–8 Hz) and gamma (30–50 Hz) frequencies or their combination such as alpha/theta ratio and beta/theta ratio (Marzbani et al., 2016; Orndorff-Plunkett et al., 2017; Pandey et al., 2012).

As mentioned, addictive behaviours result partly from an altered top-down process on craving, setting up a reduced cognitive control with impaired inhibition of the dominant response. This impairment has been attributed to abnormal neuroelectrical characteristics: a discrepancy in the N2/P3 complex component with either increased or decreased amplitudes and prolonged latencies (Campanella et al., 2014; Luijten et al., 2014; Petit et al., 2014). Given that identifying the relevant frequency patterns underlying this impairment remains difficult, researchers set out to pinpoint the most suitable NF protocol for treating SUD (Dousset et al., 2020). Since the 1980s, the most popular protocol has been Peniston and Kulkosky's protocol (modulation of alpha/theta frequencies) (Peniston & Kulkosky, 1989),

which targets a state of relaxation. By increasing alpha/theta activity while reducing β-endorphin levels, this protocol counterbalances anxiety-eliciting situations. Thus, patients are relieved from the tension linked with withdrawal in the early stages of abstinence (Peniston & Kulkosky, 1989; Saxby & Peniston, 1995). Scott and Kaiser's protocol, connecting alpha/theta regulation with SMR-beta modulation, extends Peniston's protocol to a larger panel of substances of abuse (Luigjes et al., 2019). On the one hand, alpha/theta modulation intends to soothe conditions of stress and anxiety. On the other hand, SMR-beta modulation aims to alleviate impulsivity by remediating cognitive deficits. Together, these protocols seem to have a pronounced impact on maintaining abstinence (Scott et al., 2005; Sokhadze et al., 2008; Dalkner et al., 2017). Although they have ample merit, the evolution of our knowledge regarding the underlying mechanisms of SUD provides us with the opportunity to investigate the modulation of other frequency bands (Dousset et al., 2020). For instance, as the N2/P3 complex may be viewed as an overlay of brain oscillatory components with the theta band shaping the N200 and the early part of the P300 wave, and the delta band shaping the main part of the P300 (Jones et al., 2006), a delta/theta protocol could be a promising perspective for the care of addicted patients (Kamarajan et al., 2004).

7.4.4 Neurofeedback: Future Perspectives and New Insights

Despite the conventional treatments devised for SUD, the relapse rate remains astonishingly high and outlines the limitations of the conventional systematic approach that offers medication and psychotherapy (Andersson et al., 2019). In fact, SUD induces long-lasting changes in brain functioning resulting from the interaction between chronic substance use, genetic disposition and environment. Hence, a psychiatric diagnosis must consider heterogeneous entities characterised by extremely complex changes in the brain (Perna et al., 2018). Assuming the idea of neurobiological heterogeneity within SUD, identifying biomarkers should allow us to move towards stratified psychiatry, meaning stratifying subgroups of patients' profiles paving the way to personalised medicine to provide reliable and customised assistance (Arns, 2020; Perna et al., 2018). To quote Arns et al. (2011), '… in this area the goal is to prescribe the right treatment, for the right person at the right time as opposed to the current one-size-fits-all treatments' (Arns et al., 2011). The underlying idea behind personalised medicine is that brain imaging data illustrate stable phenotypes incorporating both the effects of nature and nurture. It allows the identification of neurological biomarkers and leads to predictions regarding treatment outcomes (Perna et al., 2018). Ultimately, such insights could allow the implementation of tailor-made NF protocols related to precise alterations and should lead to a more targeted intervention, thereby fostering specific needs to be breached. For example, according to theoretical concepts, both the *incentive-sensitization theory* of Robinson and Berridge (1993) and the *dual-process model* introduced by Wiers et al. (2007) are linked to the *I-RISA (impaired response*

inhibition and salience attribution) syndrome conceptualised by Goldstein and Volkow (2002), putting forward an increased salience of drug-related cues paired with disabled inhibition of the dominant response. In that frame, and as already discussed in our review published in 2020, '… the challenge of maintaining abstinence more directly, i.e., through tailor-made experimental NF protocols targeting inhibitory control and/or attentional bias, warrants increased attention to patient particularities: some benefit more from decreasing/suppressing attentional bias, others more from increasing inhibitory control, and others instead make the most of both' (Dousset et al., 2020).

In the same vein, from a perspective relying upon this dualistic vision of inhibitory control, implementing NF protocols exclusively related to either proactive or reactive processes would lead to more targeted care, meeting a more specific need. In fact, a reactive course is involved in conflict resolution and interference resistance, while a proactive course operates as an anticipatory mechanism and avoids interference by actively maintaining the goal (Braver, 2012). Recent evidence suggests that these distinct modes of control call for both common and specific network activation patterns. More precisely, addictive-inhibited behaviours involve activating an anterior–posterior theta oscillatory network (Cooper et al., 2015). Nevertheless, imaging data put forward different modulations of this network depending on whether the task recruits a proactive or reactive state. On the one hand, a proactive neurobehavioural state is associated with a centro-parietal network involving delta–theta–beta oscillations and mostly recruiting the left putamen, bilateral parietal lobe and premotor cortex. On the other hand, reactive control seems to be strongly involved in right-lateralised frontal, parietal and temporal networks, along with alpha–theta band activity (Cooper et al., 2015; Garcia et al., 2017; van Belle et al., 2014).

Overall, from what we know, and we are still learning about NF, this non-invasive method seems attractive and promising for modulating dysfunctional brain networks associated with SUD to reduce symptoms and promote resilience. As NF is a new approach in managing psychiatric ailments, the challenge remains for establishing standardised procedures for mapping brain networks targeted with NF (Bracht et al., 2021). In this respect, all the investigations will refine our knowledge of how NF works through identifying variables and characteristics that make the NF training effective in favour of an optimal intercession.

7.5 General Conclusion

The primary aim of this chapter was to summarise the main neurocognitive interventions aimed at addressing the clinical aspects of SUDs. To the best of our knowledge, the neurobiology of addiction, that is, an overwhelming motivational drug-seeking and a low capacity to control the desire to consume, is indexed by long-lasting changes in brain function. To remodel these dysfunctional neural circuits, the development of neuromodulation techniques has evolved in response to

the enduring vulnerability to relapse even after years of abstinence. We have explicitly focused on the therapeutic potential of DBS, rTMS, tES and NF approaches in this chapter. Experimental evidence for these neuromodulation techniques demonstrated encouraging results in consolidating abstinence, highlighting the critical role of cognitive functioning in regaining control over problematic behaviours when facing stimuli predicting the availability of the substance and its use. Importantly, despite compelling arguments favouring the previously stated neuromodulation procedures, more standardised and rigorous experimental designs and objective reports are needed to consolidate efficacy (Ekhtiari et al., 2019; Fried et al., 2021; Ros et al., 2020).

In line with the recommendation of several recent reviews (Bollen et al., 2021; Dedoncker et al., 2021), to increase their efficacy, tDCS and rTMS should be combined with psychological interventions (e.g., mindfulness, cognitive training), ideally, tailored to fit distinct endophenotypes (e.g., impaired inhibitory control, low working memory) and learning. Indeed, the state of the brain at the time of stimulation can be critical for optimal clinical outcomes (Dinur-Klein et al., 2014). The 'activity-selectivity' hypothesis stresses that tDCS preferentially modulates populations of active and inactive neurons (Bikson et al., 2013). Finally, the recent recognition that the insula, a region of the cerebral cortex, is involved in various critical aspects underlying SUDs (interoception, decision-making, etc.) led us to recommend targeting this region with brain stimulation in the future (Ibrahim et al., 2019), particularly with deep TMS (Dinur-Klein et al., 2014).

Regarding neurofeedback intervention, considering the progress on our fundamental understanding of the neurobiological underpinnings of SUD, the currently enforced protocols should be kept up to date to specifically target the needs of patients presenting distinguished profiles and move towards a stratified medicine. Further, according to the current fostering discussions in this area, an important aspect of neurofeedback practice is that future studies are required to provide (1) well-controlled experimental designs, (2) objective measures of brain changes and (3) links between neurological biomarkers, cognition and clinical improvements to reliably authenticate the specific impact of neurofeedback and demonstrate robust evidence of its efficiency (Thibault et al., 2017; Micoulaud-Franchi et al., 2018; Thibault & Raz, 2018).

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Chapter 8
Alcohol Use Disorders and Psychiatric Comorbidities

Xavier Noël and Salvatore Campanella

8.1 Introduction

Impaired control on alcohol consumption, better known as alcohol use disorder (AUD), can lead to major psychological, social and physical consequences and remains a major cause of morbidity and mortality worldwide (GBD 2017 DALYs and HALE Collaborators, 2018; Grant et al., 2015). In addition to psychosocial interventions (Jaehne et al., 2012) and pharmacological trials (Miller et al., 2011) either singly or in combination (Anton et al., 2006), there is still a need to develop new complementary tools, useful for the management of AUD. A major problem in the treatment of AUD is the relapse rate (return to a severe form of AUD after abstinence or a period of controlled alcohol consumption) which is approximately 50% at 3 months and 85% at 1-year post-discharge, for recently detoxified alcoholic patients (Boothby & Doering, 2005). Along with the intrinsic complexity of addictive behaviour and various associated factors (such as genetic, epigenetic, social and cultural) that may explain the difficulty in treating and recovering from AUD, a crucial point certainly refers to the impact of psychiatric comorbidity on the detection and management of AUD. Psychiatric comorbidity (or dual diagnosis) is a crucial problem in AUD patients because it is well known to increase the risk of relapse (Bradizza et al., 2006), making therapeutic intervention more difficult (Daley & Moss, 2002; Sterling et al., 2011; Vitali et al., 2018), for example, by decreasing the treatment compliance (Dixon, 1999) or by increasing the discontinuation of treatment (Bischof et al., 2005).

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Epidemiological studies have shown a rate of 15% for dual diagnoses in the general population, which in clinical care units dealing with mental health and addiction can reach more than 8% (Flynn & Brown, 2008). This high rate is not surprising if we consider that alcohol and substance use is an independent risk factor for the development of a psychiatric illness, such as in patients with schizophrenia (Green et al., 2003). A mental disorder increases an individual's risk of subsequent alcohol drug use and dependence (Conway et al., 2016) through, for instance, the loss of psychosocial status (Kessler, 2004).

AUD is strongly associated with other psychiatric syndromes (Rehm, 2011) and is responsible for 10% of the disease burden related to substance use and mental disorders (Whiteford et al., 2013). The clinical signs characterising an AUD have been described in the last two versions (versions IV and V) of the Diagnostic and Statistical Manual of Mental Disorders (DSM).

The present chapter focused on the presence of more than one disorder in an individual over sometime (de Graaf et al., 2002). The frequent co-occurrence of AUD with other psychiatric syndromes (e.g. mood, anxiety, substance use, thought disorder, etc.) raises important questions about the potential mechanisms, which are likely to vary depending on the associated disease (Grant et al., 2004). The pathways linking AUD to psychiatric disorders are diverse including direct or indirect causal link and shared causes, and the temporal sequence of the appearance of the syndrome is of great importance, particularly for the management of patients with multiple diagnoses in psychiatric practice (Castillo-Carniglia et al., 2019). For instance, virtually all drugs abused by humans are acutely rewarding because of their actions on a final common biological pathway involving the mesolimbic dopaminergic system (MDS), and more precisely, the Nucleus Accumbens in the ventral striatum (Di Chiara & Imperato, 1988). Through direct projections, MDS neurons distribute information about the reward value of events to the brain structures, primarily involving the prefrontal cortex, which is implicated in cognitive control, a mechanism by which previously rewarded but task- or goal-inappropriate responses are inhibited (Iacono et al., 2008). In individuals with AUD, research found a suboptimal interaction between one system, encoding the reward properties of an event (acting as a reinforcement learning signal, increasing the incentive salience of a reward), and another, implicated in future-oriented processes and regulating current actions regarding the long-term goal-directed motivations (Robinson & Berridge, 2003). This decision alteration could increase the risk of developing other psychiatric disorders and/or reward-related deficiencies characterising other mental diseases can pre-exist and promote AUD (Castillo-Carniglia et al., 2019).

Based on the identification of transdiagnostic factors of psychopathology and substance use disorders (Eaton et al., 2015; Castillo-Carniglia et al., 2019), we opted to examine the comorbidity between AUD and internalising disorders (e.g. depression), externalising disorders (e.g. other substance use disorders) and thought disorders (e.g. psychosis). The study of the structure of the common mental disorders suggests that comorbidity results from underlying fundamental psychopathological processes, which are internalising and externalising problems (Krueger, 1999). Sadness, fear and rumination are implicated in internalising disorders, while

externalising disorders involve breaking rules and aggression. More recent psychopathological frameworks such as Hierarchical Taxonomy of Psychopathology (HiTOP) (Kotov et al., 2017) have characterised AUD as disinhibited externalising problem (impulsivity with negative consequences, lack of foresight, etc.) and, to a lesser extent, antagonism externalising problem (narcissistic, histrionic, paranoid, borderline personality pathology, etc.). To examine the complex clinical profiles associated with AUD, this chapter aimed to review some of the key aspects of the dimensional and categorical approaches that represent the majority of the investigations in the study of psychiatric comorbidities (APA, 2013; World Health Organization, 2018). Potential biopsychosocial mechanisms involved in the co-occurrence of symptoms, syndromes or dimensional traits were considered.

8.2 AUD and Other Externalising Associated Disorders

8.2.1 Substance Use Disorders (SUDs)

AUD and SUDs often co-occur, with almost two people with AUD having a lifetime SUD (Kessler et al., 1997). In addition, the risk of SUD in people with AUD diagnosed within the past year is three to five times higher than in those without AUD (Grant et al., 2015; Hasin et al. 2007, b). The presence of SUD in adolescence increases the risk of AUD by a factor of 3.5–4 (Farmer et al., 2016).

This association has been explained by the gateway hypothesis (Kandel & Kandel, 2015). The gateway hypothesis is based on the finding that most marijuana and other illicit drug users have a history of alcohol and tobacco consumptions for several months or years. At the neurobiological level, an increase in overall acetylation in the striatum due to nicotine and alcohol consumptions can support the gateway phenomenon (Kandel & Kandel, 2015).

The gateway hypothesis should incorporate the influence of social context, with a more pronounced engagement in alcohol consumption in connection with a higher level of opportunity for exposure to marijuana (Wagner & Anthony, 2002). Although this hypothesis is well supported by data to explain the initiation of illicit drugs after AUD, the co-occurrence of AUD and SUD remains unexplained. The concept of liability to addiction (Vanyukov et al., 2012), which is a latent characteristic including genetic, psychological, behavioural or environmental risk factors, promotes a propensity to manifest addictive behaviour (Kendler et al., 2007). For instance, half the risks of nicotine use disorder and AUD is mediated by genetic factors (Schlaepfer et al., 2008). The history of risk factors for addiction-related comorbidities is even more complex. Young adolescent males run the risk of consuming alcohol and tobacco together due to environmental factors, while the latter dual diagnosis is due to genetic risk factors (Koopmans et al., 1997). The escalation of alcohol consumption to AUD can be facilitated by tolerance to the pharmacological effects of nicotine (Adams, 2017).

Interestingly, differential impacts of alcohol and cannabis abuse have been shown in the adolescent brain (Jacobus & Tapert, 2014). AUD symptom severity is positively related to the responses of the amygdala to emotional stimuli and *negatively* related to responses of regions implicated in executive attention and response control including the dorsolateral prefrontal cortex, anterior cingulate cortex and precuneus, as a function of task performance. In contrast, cannabis use disorder (CUD) symptom severity is unrelated to the amygdala responses but positively related to responses within regions including the precuneus, posterior cingulate cortex and inferior parietal lobule as a function of task performance (Aloi et al., 2018). Such differential brain modulations should be taken into consideration at the clinical level as it strengthens the idea that AUD combined with CUD should be specifically treated as compared with AUD or CUD alone.

8.2.2 Personality Disorders

In people with a personality disorder including borderline personality disorder and antisocial personality disorder, the prevalence of AUD is massive. A previous study has reported 52% of people with borderline personality disorder suffering from self-image problems such as difficulty managing emotions (mood swings, anger, etc.) and behavioural issues (aggressiveness) and an unstable relationship pattern (fear of abandonment) have a lifetime prevalence of AUD (Guy et al., 2018), which is even higher (74%) in people with antisocial personality disorder (aggressive and abusive relationships, lack of empathy, manipulation and risk-taking issues).

The developmental pathway of AUD concerning personality disorders has not been elucidated, but personality disorder generally precedes AUD. Crucially, engagement in early alcohol use and the lack of control over alcohol consumption leading to AUD in this population reflect compromised capacities for self-regulation and self-control (e.g. behavioural disinhibition) (Cloninger et al., 1988; Verheul & van den Brink, 2000) as well as altered systems for social processes (Hanegraaf et al., 2021).

8.3 AUD and Internalising Associated Disorders

8.3.1 Major Depressive Disorder (MDD) and Anxiety Disorder

Up to one in five persons with AUD has been reported to experience MDD in the past 12 months (Lai et al., 2015). The lifetime prevalence of AUD in patients with MDD is approximately 30% (Sullivan et al., 2005). The relationship between AUD and MDD is likely to be multidirectional. In short, depressive symptoms in childhood can double the odds of DSM-IV alcohol dependence in young adults (Crum

et al., 2008). However, the likelihood of MDD in people with AUD is reported to be two times higher than without AUD, while that of AUD in people with MDD is 2.1 times higher than without MDD (Boden & Fergusson, 2011). In other words, we found evidence in favour of the self-medication hypothesis (Khantzian, 1985) and also in favour of the development of depressive symptoms due to the social and biological consequences of AUD. Finally, common genetic links between depression and AUD have also been reported in studies on twins (Lin et al., 1996), with a plausible role of exposure to shared environmental causes, as demonstrated by a relationship between a genetic risk variant and AUD among African Americans only (Zhou et al., 2017).

Regarding anxiety disorders, the prevalence of AUD ranges from 20% to 40% (Lai et al., 2015). The meaning of this association is in two ways, from AUD to anxiety disorders and vice versa. However, as pointed out in a review article (Castillo-Carniglia et al., 2019), the strength of these paths is modest. The co-occurrence of AUD and anxiety disorder is mainly due to the interaction between environmental (Maier & Merikangas, 1996) and genetic factors (Hodgson et al., 2016).

At the neural level, it is shown that alcoholic individuals with or without comorbid depression were impaired in the processing of emotions. This deficit is neurophysiologically indexed by early perceptual and later decisional alterations. In contrast, non-alcoholic patients with depression only exhibited neural decisional (not perceptive) impairments (Maurage et al., 2008). These results lead to potential implications concerning the use of event-related potentials for differential diagnosis in psychiatry, notably concerning comorbidities in alcoholism. More importantly, they also stressed the importance of managing patients with AUD alone differently from AUD patients with comorbid depression.

The relationship between alcohol use, AUD and post-traumatic stress disorder (PTSD) points to several possibilities. After a traumatic event, not necessary with PTSD, alcohol consumption generally increases (Hasin et al., 2007, b). However, the development of an AUD following trauma is associated with a drinking problem before the event, thus representing an exacerbation of the pre-existing problems (North et al., 2011).

Particularly among women, alcohol consumption is a risk factor for PTSD due to the high likelihood of sexual and other types of assaults (Strunin et al., 2015).

In summary, the association between mood disorder and AUD may reflect a feed-forward vicious cycle, where reduction in short-term anxiety in response to alcohol consumption is related to the induction of long-term anxiety due to biopsychosocial effects of chronic alcohol consumption (Kushner et al., 2000).

8.3.2 Attention-Deficit Hyperactivity Disorder (ADHD)

ADHD, characterised by attention and hyperactivity problems, is frequently associated with AUD between 19% and 26% of young adults (Romo et al., 2018). The prevalence of ADHD in adults with AUD is approximately 33% (van Emmerik-van Oortmerssen et al., 2012). Longitudinal studies highlight that children with ADHD are more likely to develop SUDs than those without ADHD, and that this increased risk is robust to demographic and methodological differences that vary across studies (Lee et al., 2011). The negative impact of ADHD on healthy behaviours, including alcohol consumption, underscores the importance of early detection and treatment of ADHD. One reason for this co-occurrence can be linked to the mutation of dopamine receptors in ADHD people, thus facilitating the consumption of alcohol, whose effects are similar to those of psychostimulant drugs (Maxwell, 2013). Deficits affecting the executive system and its prefrontal neural bases, such as poor inhibitory control, are common features of ADHD (Rubia et al., 2005) and AUD (Noël et al. 2001, b).

8.4 AUD and Thought Disorder

After nicotine dependence, AUD is the most common comorbidity in patients (Leposavić et al., 2015). The prevalence of a lifetime AUD is found to be more than twice as high in people with psychotic experiences (17.1%) than in people without a history of psychotic experiences (7.2%). Research supports the idea of a two-way relationship between AUD and psychotic syndromes (Degenhardt et al., 2018). AUD people are more likely to develop the psychotic syndrome and vice versa (Degenhardt et al., 2018). Regarding the etiological factors of the co-occurrence of AUD and psychotic symptoms, an alcohol-induced psychotic disorder in the context of alcohol dependence has been established (Jordaan & Emsley, 2014). The self-medication hypothesis is also supported, thus reflecting AUD being secondary to schizophrenia. Finally, some arguments point to an underlying form of schizophrenia triggered by excessive alcohol consumption (Castillo-Carniglia et al., 2019).

Bipolar disorder with AUD comorbidity affects about 24–44% of people (Hunt et al., 2016). One hypothesis is that AUD triggers highly inherited bipolar disorder (Rakofsky & Dunlop, 2013). Further, people with bipolar disorder are found to use alcohol as a coping strategy to reduce discomfort, but no consensus has been reached (Farren et al., 2012).

8.5 Comorbidity Research: Vision for Future Research

To date, most studies have endorsed a classification system establishing the presence or absence of a disorder (American Psychiatric Association, 2013; World Health Organization, 2018). This categorical approach has been highly contested in recent years mainly for the following reasons: (1) psychopathology exists in a continuum with normal range functioning (Kotov et al., 2017), (2) the imposition of a categorical nomenclature in naturally dimensional phenomena leads to a substantial loss of information and diagnostic instability (MacCallum et al., 2002), (3) there is limited reliability with less than 40% inter-rater reliability (Regier et al., 2013), (4) many existing diagnoses are quite heterogeneous and encompass multiple pathological processes (Clark et al., 1995), (4) comorbidity is extremely common in both clinical and community samples (Kessler et al., 2005) and (5) there exists lack of sensitivity (despite significant distress, many patients did not meet the criteria for any disorder). The main consequences of the categorical classification of the dimensional structure of psychopathology are the slow pace of discoveries in psychiatry (Hyman, 2010) and poor help in the selection of treatment it provides (Beutler & Malik, 2002).

Despite the recent progress of the DSM-5 and the International Classification of Diseases 11th revision, in overcoming some of these limitations (Clark et al., 2017), the resolution of the weaknesses of traditional taxonomies is emerging in the form of a quantitative nosology, an empirically based organisation of psychopathology (Castillo-Carniglia et al., 2019; Insel et al., 2010; Kotov et al., 2017; Michelini et al., 2021). In the diagnosis of SUD, dimensionality is strongly supported by scientific data (Hasin et al., 2013). Two important dimensional classification systems of psychopathology, the Research Domain Criteria (RDoC) framework by the National Institute of Mental Health (Cuthbert & Insel, 2013; Insel et al., 2010) and the HiTOP, have emerged (Kotov et al., 2017; Michelini et al., 2021). The RDoC framework is operationalised in the RDoC matrix representing eight units of analysis (genes, molecules, cells, circuits, physiology, behaviour, paradigms and self-reports). The rows represent constructs grouped into six higher-level domains, including negative valence systems, positive valence systems, cognitive systems, systems for social processes, arousal/regulatory systems and sensorimotor systems. The HiTOP system consists of a hierarchical organisation framework describing general dimensions (e.g. p-factor) (Caspi & Moffitt, 2018), specific dimensions of symptoms and maladaptive behaviours (e.g. AUD), highly correlated components forming larger dimensional syndromes (e.g. relief from drinking) and closely related syndromes defining subfactors and associated subfactors from spectra (e.g. externalising, antagonistic externalising and disinhibited externalising in AUD) (Helle et al., 2020).

The general idea is to improve our understanding of complex psychopathological profiles by integrating them into a dimensional framework reflecting a clinical profile comprising many symptoms and several (categorical) syndromes. Conceiving symptoms rather than syndromes within a certain network is also a promising

direction for the future (Borsboom et al., 2018). This network model assumes that current symptoms are directionally caused, thereby implying that intervening in one or several key symptoms in the network can prevent a broader cascade of psychopathology.

Taken together, the categorical approaches of psychopathology emphasise that AUD often coexists with other psychiatric entities. Currently, dimensional and network modelling in psychopathology offers a new horizon for research that can considerably improve the treatment of AUD in association with non-AUD symptoms and syndromes.

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Chapter 9
Interoception and Addiction: Etiological Mechanisms and a Root for Intervention

Laura Angioletti and Michela Balconi

9.1 The Construct of Interoception as a Dynamic Multicomponent "Interoceptive Experience"

Interoception refers conventionally to the afferent processing of signals that originate within the body and refer to the state of the body (Craig, 2002). It is the mechanism by which the nervous system detects, interprets and integrates the signals that come from inside the body, providing a punctual and complete mapping, moment by moment, of the internal body condition, through the conscious and unconscious levels (Tsakiris & De Preester, 2018). It includes most of the body signals, such as information that is relevant for homeostatic control and physiological needs (hunger, thirst, heat, pain), the signals processed at the level of the central nervous system (CNS) that provide information on the general state of the body (i.e., on the state of health and disease), as well as the neural and mental representation of the internal changes of the body.

Interoceptive signalling has been considered a process composed of several elements, encompassing reflexes, impulses, feelings, drives, adaptive responses, and cognitive and emotional experiences; and it has been previously highlighted how it contributes to the maintenance of homeostatic functioning, body regulation and survival (Pace-Schott et al., 2019). Also, the representation of bodily responses informs different states of subjective experience that affect the motivated approach or avoidance behaviour towards environmental stimuli (Ateş Çöl et al., 2016), and

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may contribute to emotion-specific feelings (Critchley & Garfinkel, 2017). Accordingly, it is possible to consider the complex interplay between mind and body as a dynamic multicomponent "interoceptive experience" (Angioletti & Balconi, 2020; Balconi & Angioletti, 2020, 2021).

In line with this broad definition of the construct, interoception consists of different dimensions ranging from the body afferent signals to the behavioural and metacognition level (Tsakiris & De Preester, 2018, p. 127). Indeed, interoceptive sensitivity (IS) and interoceptive accuracy (IAcc) are the firsts dimensions commonly quantified by measuring a person's ability to perceive and accurately report one's heartbeats at rest (controlled for instance through the Heart Beat Detection task; Schandry, 1981; Tsakiris & De Preester, 2018); secondly, the dimension of interoceptive awareness (IAw) corresponds to subject's confidence in his/her own behavioural performance accuracy (i.e., the confidence-accuracy correspondence, the insight into performance aptitude corresponding to metacognitive accuracy); finally, the higher-level dimension (going beyond metacognition, namely executive attribution) includes the executive processes like the modulation of attention or the shifting from interoceptive to exteroceptive attention (e.g., within dual tasks or between tasks) (Critchley & Garfinkel, 2017; Tsakiris & De Preester, 2018). At each dimension, individual differences manifest themselves and can have an impact on emotional processes and states; moreover, these dimensions are thought to interact with each other (Tsakiris & De Preester, 2018).

With respect to the link between IAcc and IAw, the "interoceptive sensitivity hypothesis" (Tyrer, 1973) posited that IAw goes in parallel with IAcc, since individuals with a high awareness level (IAw) showed highly accurate perceptions of bodily sensations (IAcc), evidence specifically demonstrated in patients with clinical anxiety and panic disorder (Ehlers & Breuer, 1992). However, recent research has led to a more differentiated theoretical model of interoception processes (Garfinkel et al., 2015; Tsakiris & De Preester, 2018), stating IAw can be accompanied by an accurate perception of bodily sensations, but such accuracy is not necessarily implied (Calì et al., 2015).

Moving into the context of addiction, several authors before highlighted the crucial role of interoception, given its homeostatic function, in the onset and maintenance of addictive behaviour (Koob & Moal, 2001). Drug addiction is a multifaceted clinical and psychological condition characterized by a complex interplay of biological processes, including changes in the mesolimbic system. According to modern neurocognitive models, drug abusers and consumers, in fact, have distinct activation and/or adaptive connectivity patterns affecting the insular cortex (Ding & Lee, 2013; Ma et al., 2015; Naqvi et al., 2007; Sutherland et al., 2013), a putative interoceptive centre (Craig, 2002). The insula cortex is hypoactive during cognitive regulation tasks of addiction, but hyperactive when confronted by addiction-related stimuli (Kemp, 2020; Paulus & Stewart, 2014). Blunted anterior insula activation (Berk et al., 2015; Migliorini et al., 2013; Stewart et al., 2020) and impairment in multiple interoceptive dimensions, including subjective interoceptive sensations and IAw, were found in patients with SUD (Ateş Çöl et al., 2016; Bergquist et al., 2010; Schmidt et al., 2013).

Previous studies conceived the first interoception dimensions (i.e., IS, IAcc and IAw) as relatively stable traits which can modulate the subjective experience of emotion; on the other hand, recent research showed that the different dimensions of interoception can be instead modulated by specific training (Farb et al., 2013b), such as awareness-based approaches like mindfulness-based interventions (MBIs), slow breathing (Weng et al., 2021) and the degree to which a person focuses the attention on bodily changes (Farb et al., 2013a, b). This training will be better described in the next sections of this chapter.

In our opinion, two of the most interesting and least studied aspects of interoception, in general terms, are: (a) the higher-level dimension of the construct (IAw and executive attribution), suggesting the link between the attention to the bodily signals and executive functioning; (b) the possibility to modulate and manipulate interoception through specific training. The reasons why we believe that these aspects are also of interest to the context of addictions will be described in the next three sections which will focus on the dysfunctional interoceptive processing in addiction disorders, shared neural basis between interoception, addiction and executive functions (EFs), and on interoceptive manipulations as a basis of the interventions in addiction disorders. But before discussing the training opportunities involving interoceptive modulations, it is relevant to explore the relationship between interception and addiction in the next paragraph.

9.2 Dysfunctional Interoceptive Processing and Addiction Disorders

In the context of mental health, dysfunction of interoception is increasingly recognized as an important component of several mental health conditions, including anxiety disorders, mood disorders, eating disorders, somatic symptom disorders and addictive disorders (Bonaz et al., 2021; Khalsa et al., 2018). Substance addiction, among these conditions, is characterized by interoceptive impairments and abnormal reactions to interoceptive cues (Avery et al., 2017; Goldstein et al., 2009; Naqvi & Bechara, 2009; Paulus et al., 2013); therefore, abnormalities of interoception are now recognized to occupy a central role in the conceptualization of addiction.

Relatively recent works have begun to explore the relevance of this construct to drug addiction for at least three reasons:

- The first concerns the fact that drugs of abuse and drug-related stimuli induce pronounced peripheral changes, and damage to brain regions known to support interoception (Stewart et al., 2020; Verdejo-Garcia et al., 2012);
- The second is that the ability to correctly perceive and integrate interoceptive signals has a link with withdrawal and relapse;
- The third is that individuals with impaired interoceptive abilities can be predisposed to develop SUD (Ateş Çöl et al., 2016) and BAs.

Therefore, it follows that the interception can be closely linked to the development and maintenance of an addiction and that it can play the balance between health and pathology. Following the metaphor of the balance, a theoretical account of SUD and BAs (specifically gambling) has proposed that addictive behaviours are the product of an imbalance between three separates, but interacting, neural systems:

– An *impulsive system*, largely amygdala–striatum dependent, a neural system that promotes automatic, habitual and salient behaviours;
– A *reflective system*, mainly prefrontal cortex dependent, a neural system for decision-making, forecasting the future consequences of a behaviour and inhibitory control;
– The *interoceptive system*, the insula that integrates interoception states into conscious feelings (such as urge and craving), that in turn plays a strong influential role in decision-making and impulse control processes that are involved in uncertainty, risk and reward (Noël et al., 2013a).

These systems account for poor decision-making (i.e., prioritizing short-term consequences of a decisional option) leading to more elevated addiction risk and relapse both in SUD and BAs. This triadic neurocognitive model for addiction has been briefly described in Chap. 4 of this book, and neural evidence for these three systems has been provided. Here, special attention will be given to the third system of the model, that is, the *interoceptive system,* which transforms bottom-up bodily sensations into a subjective state of craving, accordingly, boosting the impulsive system and/or weakening the normal functioning of the reflective system.

Brevers and Noël (2013) described the interoceptive processes as mechanisms translating bodily signals into feelings of desire, anticipation or urge, with a halfway role between the initiation and maintenance of addiction (Goldstein & Volkow, 2011; Goldstein et al., 2009). Furthermore, Paulus et al. (2009) in a previous contribution also argued and stressed that the body state, as defined by the integration of interoceptive information, is a crucial arbiter of the risk of onset and transition to the compulsive use of substances that are addictive. In fact, individuals at risk of developing an addiction are characterized both by an effectively altered internal body state and by an altered perception of their internal body state over time, which lead to a change in hedonic and incentive motivational properties of the addictive substance.

Specifically, individuals with addiction disorders experience *alliesthesia* of interoceptive processing (i.e., they experience the psychophysiological phenomenon for which rewarding properties of stimuli are dependent on the internal state of the individual). The person confronted with the same stimulus can therefore perceive it as pleasant or unpleasant based on the changes of the internal state. A common example from another domain may be that food tastes better when we are hungry. In general, a stimulus capable of improving the state of the interior of our body will be perceived as pleasant. On the contrary, a stimulus that disturbs the internal state of our body will be perceived as unpleasant or painful. The physical pleasure internal experience derived by drug assumption leads to increased

incentive motivational properties of the drug over time, thereby augmenting the probability of subsequent use (Paulus et al., 2009).

To better explain this point, it is necessary to take a step back. The two circuits of the reward systems' neural pathway—the dopaminergic mesolimbic circuit associated with incentive salience and the more distribute system that produces the hedonic experience of reward—generate interoceptive sensations that are felt as urges/craving and physical pleasure, respectively (Berridge & Kringelbach, 2015). Both these "physiological feelings" play a key role in maintaining addictive behaviour (Pace-Schott et al., 2019; Paulus et al., 2009; Paulus & Stewart, 2014). In particular, the modified physiological conditions that arise as a result of taking a substance and developing an addiction can alter the reward value of stimuli (*allies-thesia*) in such a way that behaviours that previously would have been considered adverse or neutral become rewarding (Paulus et al., 2009). For example, excessive stimulation of reward circuitry may promote continued drug use to avoid negative states (negative affect, stress or anxiety).

Furthermore, some recent theoretical discussions (Goldstein & Volkow, 2011; Goldstein et al., 2009) propose that the inability to grasp the interoceptive signals can also affect the EFs, specifically decision-making and metacognitive capacity [i.e., the ability to reflect on one's own actions and thoughts, but also to assess one's own performance at the behavioural level, discriminating its success or failure (Cleeremans et al., 2007); for this concept, see also Chap. 1] in individuals with addictions. The deficiency of metacognitive capability in addicts has been well documented, and it is extremely relevant for the clinical relapses, since the individual fails to understand the seriousness of the condition (Goldstein et al., 2009). The underestimation of addiction severity and a disconnection between self-perception (even at the bodily level) and actual behaviour have been detected in different categories of substance users (cocaine, nicotine, methamphetamine and cannabis users) (Chiu et al., 2008; Hester et al., 2009; Moeller et al., 2010; Payer et al., 2011); as well as in BAs, both Gambling Disorder (GD). (Brevers et al., 2013; Brevers & Noël, 2013) and Internet Gaming Disorder (IGD) (Casale et al., 2021). Taken together, this evidence highlights the link between interoceptive processes, reward systems and EFs (decision-making and metacognitive ability) in individuals with addiction.

9.3 Neural Basis of Interoception: Shared Circuits with Addiction and EFs?

Interoception and its neural basis in relation to addictive disorders have been described in previous reviews of the literature (Naqvi & Bechara, 2010; Paulus et al., 2013). Indeed, the development of addiction is dependent on a variety of neuroadaptive processes, including those affecting the reward system and cognitive control mechanisms (Koob, 2013). Recent models also suggest that interoceptive

experiences are essential for the processing of sensory signals linked to pleasure and craving (Volkow & Morales, 2015), two key components of reward and addiction. For instance, anticipatory interoceptive markers including cocaine peripheral effects (Kiyatkin & Brown, 2007) have been shown to function as a peripheral interoceptive conditioned stimulation (Wang et al., 2013), leading to cocaine reward and seeking in animal experiments. These findings indicate that associative learning between peripheral and rewarding effects can be facilitated by exposure to interoceptive signals during drug intake. As a result, long-term drug use can modulate interoceptive pleasure-related pathways (Volkow & Morales, 2015), and can be associated to neuronal adaptations (Cheng et al., 2007).

According to neuroimaging research of drug addicts, the insula is the hub that integrates interoception states into conscious feelings (such as urge and craving), that in turn plays a strong influential role in decision-making and impulse control processes; this CNS centre for processing and integrating interoceptive signals is hypoactive during cognitive control processes but hyperactive during cue reactivity and substance-specific, reward-related processes (Naqvi & Bechara, 2010).

The schematic model of Naqvi and Bechara (2009) on how the interoceptive functions of the insula contribute to substance use motivation illustrated how the insula plays a crucial role in pathways strictly related to the prefrontal cortex (PFC) portions and EFs.

Firstly, the insula represents the interoceptive effects of drug use rituals. This results in a distinct subjective quality of the drug-taking ritual, which involves conscious recognition of the interoceptive effects as well as satisfaction and satiety (i.e., reward). The dopamine release, which is triggered by the drug's effects on the CNS, can modulate the reward derived from the drug's interoceptive effects, as well as drive the learning process that makes these effects pleasurable and desirable [through the amygdala and ventromedial prefrontal cortex (VMPFC)].

Secondly, the exposure to drug stimuli reactivates the representations of the interoceptive signals related to the drug use rituals through the VMPFC and amygdala. This gives rise to a subjective sensation of conscious impulse which is rooted in memory for these interoceptive effects, and which involves the activation of the insula. The Nucleus Accumbens (NAcc), which plays a role in initiating and invigorating motivated acts or the achievement of rewards (as we underlined in previous chapters), is fuelled by this representation. Together with the dorsolateral prefrontal cortex (DLPFC), which directs attention and keeps representations of specific goals in mind (e.g., the drug goal versus other adaptive goals), this mechanism produces a goal-directed action aimed at initiating the drug use ritual, whose interoceptive effects are typically integrated within the insula. The anterior cingulate cortex (ACC) contributes to conscious urges by associating the representations of interoceptive states within the insula with the representations of environmental cues that caused these states, as well as by tracking conflicts between the drug use and other goals (processed by the DLPFC).

According to the authors, the physiological signals perceived in conditions of abstinence from the substance (i.e., craving, urge) can modulate the rewarding properties of the substance, motivation and goal-directed behaviours towards

consumption, precisely through the insula (Naqvi & Bechara, 2009). Therefore, in the context of addiction, it has been proposed that the modulation of approach or avoidance behaviour towards drug use (i.e., the decision whether to assume the substance) could be mediated by interoception that incorporates an "embodied" experience of drug use (strongly characterized by bodily signals) together with an evaluation of the internal state of the individual (the individual's predicted and desired internal state versus actual internal state) (Khalsa et al., 2018; Paulus et al., 2013).

If up to this point it has been clarified how the insula plays a crucial role in the interoceptive processes and the development and maintenance of an addiction, it is worthwhile to better underline the shared mechanism between interoception and EFs. A neural network that can bridge interoception and EF is the salience network, which encompasses the anterior insula, the ventrolateral PFC and the dorsal ACC and is implicated in detecting events and providing signals to the executive control network to engage in goal-directed action (Dosenbach et al., 2007; Menon & Uddin, 2010). Within this circuit, the anterior insula may play a key role in bottom-up detection of salient events, mediating complex interactions between multiple brain networks involved in externally focused attention and internally oriented cognition (such as working memory) (Simmons et al., 2013), with its primary purpose being to flag important events for further processing (by modulating autonomic reactivity for these stimuli), in order to initiate appropriate control signals and/or to facilitate rapid access to the motor system (through the ACC) (Menon & Uddin, 2010) for implementing an action.

The addiction models integrating interoception thereby provide new potential targets for interventions that are aimed at changing the internal state that puts the individual at risk for continued substance use and dysfunctional behaviours. Indeed, they open the possibility of different types of interventions targeting the reward system and the EFs via interoceptive manipulations. Firstly, one may be able to modulate the embodied experience by enhancing insula reactivity where necessary or attenuating it when exposed to drug-relevant cues. Secondly, one may be able to reduce the urge to act by increasing the frontal control network, that is, inhibiting the urge to use by employing cognitive training, or training metacognitive abilities (Paulus et al., 2013).

In the next section, the potential modalities to train interoception in the treatment of SUD and BAs will be discussed.

9.4 Interoception as a Root for Interventions in Addiction Disorders

As described in the previous paragraphs, there is emerging evidence that individuals with addiction disorders have dysfunctions in brain systems that are important for interoceptive processing and executive functioning, which include, among others, the insula and the ACC. Individuals with addiction disorders seem to not expend

enough neural effort to process interoceptive state perturbations but may overactivate these systems while processing drug-related stimuli. As a result, inadequate detection and processing of interoceptive state changes can lead to insufficient anticipation and preparation to adapt to environmental challenges, such as responding appropriately to salient drug-related stimuli or adapting to abstinence in the presence of withdrawal symptoms (Paulus et al., 2013).

At the basis of intervention, there is the concept and evidence that interoception is a multifaceted construct that can be modulated by different methods and approaches. According to recent evidence, interoceptive pathways may be manipulated at various levels to develop interventions to improve symptoms in a range of disorders (Weng et al., 2021). Primarily via the respiratory system, various pathways can be manipulated at neural, behavioural and psychological levels to change the representation of and attention to interoceptive signals, which can alter interconnected physiological systems and improve functioning and adaptive behaviour. Also, interventions can alter interoception via neuromodulation of the vagus nerve, slow breathing techniques to change respiratory rate and depth, or awareness processes such as MBIs. It is worth noticing that all these interventions act on the person's executive control directly or indirectly and at a conscious or unconscious level.

Here, we have collected some strategies to target the interoceptive system as potential treatments for drug addiction. In general terms, there are at least four pathways to consider, which are not mutually exclusive, and that foresee the modulation of interoception as a potentially interesting medium to treat addiction.

Firstly, Noël et al. (2013b) underlined the need for "personalized" clinical model-based interventions targeting interactions between implicit processes, interoceptive signalling and supervisory function aimed at helping individuals become less governed by immediate situations and automatic prepotent responses, and more influenced by systems involved in the pursuit of future valued goals.

Secondly, it is suggested that MBIs can modulate both interoceptive function and insular activation patterns, and here we will discuss briefly the evidence derived from Price et al. (2012, 2019) research on the effects of mindful awareness in body-oriented therapy (MABT) in addiction.

Thirdly, there is emerging literature showing that the regulation of physical exercise in the brain involves the insula and ACC, and that intense physical exercise is associated with insula changes that may provide a window to attenuate the increased interoceptive response to drug-related stimuli.

Fourthly, given that preclinical and human research indicates an important overlap between the neurocircuitry regulating addiction and those regulating hunger, appetite and pathological eating behaviours, it is also possible that patients with SUD may be treated via manipulations of other interoceptive systems such as the hunger system (involved in the sense of craving) (Moore et al., 2017). Furthermore, medications approved to treat patients with addiction often have effects on hunger, appetite and food intake (Leggio et al., 2011).

9.4.1 The Reason for "Personalized" Clinical Model-Based Interventions for Controlling Interoceptive Signals

The application of different types of intervention in SUD is not mutually exclusive; however, in the perspective of "personalized" clinical model-based interventions (Noël et al., 2013b), it is useful to propose the patient with the treatment from which he/she could benefit most. Through precision medicine, a need also underlined in Chap. 5 dedicated to cognitive training, it is possible to map which are the dysfunctional domains or the compromised brain areas of the patient and, accordingly, to propose a tailor-made training. With this principle in mind, we briefly describe two types of approaches, one of which is more focused on the modulation of interoception as an embodied experience and the second one on the awareness, cognition and insight into the interoceptive effects that the substance has on the body.

Given that the increased tendency for substance use may also emerge from a highly embodied experience lived through the insular cortex activation, this mechanism may overwhelm the cognitive control system by providing a highly emotionalized physical experience (e.g., intense bodily state of substance-related craving) and by sensitizing substance abusers to the conditioning of interoceptive drug effects (Naqvi & Bechara, 2009; Verdejo-Garcia et al., 2012). Therefore, firstly, individuals with addiction disorder might benefit from interoception-modifying techniques, such as mindfulness exercises, biofeedback, interoceptive exposure therapy or physical exercise, in order to train reappraisal of the significance of bodily feedback triggered by addiction-related cues (Noël et al., 2013b; Verdejo-Garcia et al., 2012).

In addition, individuals with addiction can also benefit from therapies aimed at improving insight and metacognitive skills, since an impairment of the interoceptive system may also impair self-awareness (Goldstein & Volkow, 2011; Goldstein et al., 2009). For instance, a brief insight-related intervention (5 sessions in 2 weeks; 15 min per session aimed at increasing conscious recognition of symptoms associated with alcohol use) increased participants' will to abandon their alcohol-related actions, in recently abstinent alcohol-dependent patients (Kim et al., 2007). These findings indicate that a high degree of insight has a beneficial impact on the diagnosis process, treatment motivation and substance-related behavioural improvement, and may be important in the recovery process. Training interventions connecting interoception and metacognition in addiction disorders are particularly interesting and deserve to be better explored by future works, because they constitute an interesting way through which the implicit (interoceptive) level, if made explicit (through metacognitive reflections), can positively affect the clinical outcomes.

9.4.2 *Mindful Awareness in Body-Oriented Therapy (MABT) for Training Interoceptive Awareness Skills*

Training IAw is a promising behavioural approach for improving SUD treatment. Interoceptive training is designed to build skills in processing and managing sensory input from the body, including sensing, interpreting and integrating information about the body (Khalsa et al., 2018), as a means for reducing emotion dysregulation and the associated substance use behaviour patterns that can negatively impact treatment outcomes.

Importantly, interoception is recognized as a central mechanism that may underlie mindfulness-based approaches for SUD treatment (see Chap. 6 for MBI approaches to addiction). Mindfulness-based SUD research has demonstrated reductions in substance use and related health outcomes (Garland & Howard, 2018). However, MBIs are typically taught in a group context and do not specifically target and develop interoceptive capacity, an identified gap in SUD treatment research (Noël et al., 2013b; Paulus & Stewart, 2014; Verdejo-Garcia et al., 2012).

Mindful awareness in body-oriented therapy (MABT) feasibility as a novel adjunct to SUD treatment was previously tested by Price et al. (2012). As an individual therapy, MABT combines manual and brain-and-body approaches to develop interoception and self-care tools for emotion regulation. MABT is unique among mindfulness-based approaches in its use of touch to promote and develop the capacity for interoceptive awareness. As a therapeutic approach delivered individually, regulatory responses to sensory experience are assessed, and any difficulty with interoceptive processing is explicitly addressed through a combination of mindfulness instruction and psychoeducation (Price & Hooven, 2018). Previous findings highlighted the acquisition of interoceptive awareness skills, improved emotion regulation (self-report and physiological), reduced depression and perceived benefits of this approach among women in treatment (Price & Hooven, 2018).

As first experimental evidence in the context of SUD, a two-group randomized controlled trial repeated-measures design was used to compare MABT to treatment as usual (TAU) on relapse to substance use and related health outcomes. Participants randomized to MABT received 8 weekly MABT sessions (Price et al., 2012). Results showed significantly fewer days on substance use, as the primary outcome, for MABT compared with TAU at post-test. Secondary outcomes showed improved eating disorder symptoms, depression, anxiety, dissociation, perceived stress, physical symptom frequency and bodily dissociation for MABT compared with TAU at the 9-month follow-up (Price et al., 2012).

More recently, with the aim of decreasing craving and substance use, while increasing IAw and emotion regulation, Price et al. (2019) involved a larger group of SUD patients that were randomly assigned to one of three study conditions TAU + MABT, TAU + Women's Health Education (WHE) and TAU only. Substance use improved significantly for MABT versus TAU at 6 and 12 months. Positive longitudinal effects on secondary outcomes for MABT were evident on respiratory sinus arrhythmia (RSA), a physiological index of emotion regulation; on craving and on interoceptive awareness skills. Analyses based on participants who completed more

than 2/3 of the intervention sessions revealed additional immediate significant improvements for MABT versus TAU and WHE on depressive symptoms and emotion regulation difficulties and longitudinal improvement on mindfulness skills. Results show MABT to be efficacious for longitudinal health outcomes to support patient's recovery as an adjunct to community-based SUD treatment.

In conclusion, it is feasible to implement MABT in SUD treatment, and results suggest that MABT is worthy of further efficacy testing. Future studies could also explore this intervention on patients with BAs, and test whether MABT could positively impact the EFs domain and the neural correlates of interoception.

9.4.3 Physical Exercise for Empowering Interoception and Cognitive Control

Physical exercise's effectiveness and mechanisms in people with SUD are the subjects of a growing body of research. Exercise's ability to promote dopaminergic transmission and reverse drug-induced changes in the reward pathway may explain its beneficial effects as an adjunct in the treatment of SUD, as recently reviewed in a previous work (Lynch et al., 2013).

Indeed, acute exercise has been shown to minimize alcohol cravings (Ussher et al., 2004), tobacco cravings (Janse Van Rensburg et al., 2012; Roberts et al., 2012) and daily cannabis use (Buchowski et al., 2011). Individuals that exercise demonstrated decreased motivation to smoke and attenuated brain activity in limbic areas in response to smoking-related stimuli in comparison to those who did not exercise (Janse Van Rensburg et al., 2012), as well as an increase in default-mode activation (Janse Van Rensburg et al., 2009). However, further research is needed to determine the exact cognitive and neural mechanisms that lead to exercise's beneficial effects on drug-taking behaviour in people with SUD. One possibility regards interoceptive neural correlates and is that the ACC becomes better prepared to respond to body-relevant information triggered by drug-relevant stimuli as a result of the sustained engagement of controlled goal-directed behaviour. Accordingly, exercise can affect cognitive control mechanisms that are essential in drug addiction (Paulus et al., 2013).

To conclude, the conceptual basis of interoceptive dysfunctions in drug addiction as well as the experimental evidence of MBIs and exercise offers a valuable approach for developing new treatments for drug addiction.

9.5 Conclusion

In this chapter, we moved from the theoretical models to intervention practices in the context of addiction disorders, discussing the potential of the modulation of interoception conceived as a dynamic multicomponent construct. The neurocognitive models proposed here showed shared neural mechanisms between

interoception, addiction and EFs, suggesting the link between the attention to the bodily signals and executive functioning. Of particular interest, these models provide new potential targets for interventions that are aimed at changing the internal state that puts the individual at risk for continued substance use and dysfunctional behaviours.

Indeed, they open the possibility of different types of interventions targeting the reward system or the EFs via interoception. By conceiving interoception as a root for interventions in addiction disorders, various main pathways, which are not mutually exclusive, have been described here without claiming to be exhaustive: a "personalized" clinical model-based intervention targeting interactions between implicit processes, interoceptive signalling and supervisory function; a specific MBI can modulate both interoceptive function and insular activation patterns, that is MABT; and the regulation of physical exercise as a window to attenuate the increased interoceptive response to drug-related stimuli.

Recent trends in neuroscience are starting to further develop research in the field of interoception modulation, and new types of intervention that simultaneously focus on the brain–body axis could be useful in the field of addiction. Among the aspects to be explored by future research, it was previously suggested that current addiction interoception models may be improved by taking into account (a) the multiple components of the bodily feedback system (signal, perception and appraisal), as well as (b) how individual differences in these three components influence cognitive–affective processing in addiction (Verdejo-Garcia et al., 2012). Considering the role of EFs in SUD and BAs, interventions aiming at enhancing insight and metacognitive abilities via interoception are particularly interesting and deserve to be better explored by future works.

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Chapter 10
New Addictions in Youth: Internet Addiction and Internet Gaming Disorder

Luca Milani

10.1 Introduction: Technological Addictions in Youth

The technological development and the changes in society have modified the habits of youth and their channels of communication. Thus, in the timeframe comprised between puberty and young adulthood, new technologies exert a significant effect on psychosocial development. New technologies are ubiquitous in everyday life: More than four and a half billion people are connected to the Internet, and about half of the world's population regularly use social networks (Statista, 2021). Moreover, in the world there are more than two billion video gamers as of 2020 (Newzoo, 2020) with forecasts to reach three billion in 2023 (Wijman, 2020).

At the beginning of the "www era", scholars and researchers started to study the potential negative outcomes of excessive engagement with new technologies. The psychiatrist Ivan Goldberg proposed the term of "Internet Addiction Disorder" in 1995, as a mean to address ironically the stiffness of DSM-oriented[1] diagnoses. He intended to create a "factitious" disorder combining diagnostic criteria from substance abuse with the (at the time) novelty of the Internet. As cited by Dalal and Basu (2016), Goldberg literally (and unintendedly) opened a Pandora's Box, as his bulletin board was flooded with requests from people reporting their problems with Internet and seeking help. Since Goldberg's inception, scholars focused upon studying the potential maladaptive outcomes of interacting with new technologies, and a

[1] DSM: Diagnostic and Statistical Manual of Mental Disorders.

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good part of them addressed youth, as will be shown in Sects. 10.2 and 10.3, focused respectively on Internet Addiction (IA) and Internet Gaming Disorder (IGD).

Uncontrolled and excessive use of new technologies can lead to maladaptive outcomes in many domains and is often characterized by a subjective awareness of the problem, although this seldom translates into a request for help. In most instances, in fact, is a parent, or a significant adult (i.e., relative, teacher) to seek help for the child or the adolescent (Peter et al., 2020). In these instances, the risk is substituting "real" relations and interactions with social contacts mediated by Internet and/or online gaming activities, virtualizing the satisfaction of basic developmental needs. This dynamic seems to be more salient in the light of the recent Covid-19 pandemic, as the social distancing increased the risk of addiction (Paschke et al., 2021; Sun et al., 2020).

The risk for children and adolescents is to become socially disengaged from the "offline" relevant others due to a preference for online relations, and to jeopardize the acquisition and consolidation of those social skills that are essential in offline interactions (e.g., speaking in public, sustaining eye gaze, self-presenting to others, reinforcing others' positive attitudes, etc.). Section 10.4, thus, will cover the characteristics of youth at risk of addiction, focusing specifically on the risk factors.

There is also a growing body of studies that focus on the neurobiological correlates of new addictions, highlighting both potential risk factors of these ailments and the existence of cerebral alterations correlated with uncontrolled use of technology. Section 10.5 will briefly present the main findings of the literature.

Finally, Sect. 10.6 will cover the treatment of the technological addictions, which at the moment is largely at an experimental stage. Nonetheless, some preliminary indications can be drawn, especially as regards integrated protocols of treatment.

10.2 Internet Addiction

Kimberly Young was the among first authors to report a case study of a 43-year-old homemaker that lost control on her use of the Internet despite being "technologically illiterate" (patient's definition). It was 1996, and the echo of Ivan Goldberg's provocative yet ironic article was strong. Young (1996) reported that the woman peaked 60 h per week of connection time and was fuelled by the participation to a specific chat room where she felt a sense of community and belonging. The woman reported to feel irritable, anxious and depressed when she could not connect to the Internet. Progressively, she retired from her usual activities, diminished her contacts with family members and friends, to the point of stopping daily chores such as cleaning the home and cooking food. Her Internet-related habits impacted family relations and fuelled conflicts with her husband and her adolescent daughters. Nonetheless, the woman did not perceive her behaviour as problematic. One year after Young's report, the woman was separated from her husband and was detached from her daughters.

Young was also among the first researchers to systematize the tentative diagnosis of Internet addiction, following up her 1996 article with a research report that hypothesized Internet addiction as an impulse-control disorder not requiring a substance, and providing a batch of diagnostic criteria derived from pathological gambling (Young, 1998). In a parallel effort, Griffiths (1995) was publishing his paper about technological addictions, setting the stage for a branch of studies that focused on the potential pathological side of human–machine interaction.

Following Young's and Griffith's papers, a batch of empirical studies started to address prevalence of the phenomenon, explorations of psychosocial and psychiatric correlates and validations of various assessment instruments (Griffiths et al., 2016b).

As regards specifically the studies with youth, literature shows that Internet addiction is correlated with several factors, adverse developmental outcomes and psychopathology (for a complete review, cf. Kuss et al., 2014).

Internet addiction in youth seems to be associated with the following demographic factors: higher family income, male gender and being migrant. Some other factors (e.g., living in city or rural areas) were less clear in terms of association. Regarding Internet patterns of use, youth at risk of addiction is characterized by earlier age of Internet access, the use of Internet for entertainment, higher frequency and duration of use, the use of online video games and lower parental monitoring.

As concerns psychosocial factors, Kuss et al. (2014) highlight that youth at risk of addiction is characterized by the use of Internet for regulating the mood (and more in general by the preference for maladaptive coping, cf. Milani et al., 2009), a lower life satisfaction, the sense of being lonely, the preference for online social interactions (POSI, cf. Caplan, 2003), the sensation and novelty seeking and some personality traits (i.e., introversion, low agreeableness, low emotional stability, low conscientiousness). As regards concurrent psychopathology, Kuss et al. (2014) primarily report substance abuse, depression and suicidal ideation, ADHD, social phobia and antisocial/aggressive behaviours.

In terms of prevalence, Durkee et al. (2012) reported an aggregate European rate around 4.4%, higher for males (5.2%) than females (3.8%). Rates from other areas of the world show wider brackets (cf. Kuss et al., 2014): from 1.7% of male and 1.4% of female Finnish adolescents (Kaltiala-Heino et al., 2004) to 26.4% of male adolescents and 26.7% of female adolescents in Hong Kong (Shek & Yu, 2012).

A recent field of study concerns the correlation between Internet Addiction and sleep problems. Previous literature showed that a strong correlation exists between the two problems, but also that the direction of the correlation is not clear (cf. Tavernier & Willoughby, 2014). Chen and Gau (2016) showed that technological addiction can be indeed caused by sleep problems: insomnia and dyssomnia predict Internet Addiction at a later stage, probably due to the use of smartphones and tablets when getting asleep is difficult. In turn, adjusting to the use of devices in nighttime heightens the risk of subsequent addiction.

Ultimately, however, the scientific debate is orienting towards the abandonment of Internet addiction as a viable construct per se (i.e., being addicted to Internet could be equivalent to diagnose an alcohol addict as being addicted to Pubs or

Liquor Stores, as Internet is a mean of delivering contents; cf. Starcevic, 2013 for a critique), shifting towards a paradigm favouring the diagnosis of specific addictions related to functions of the web. Internet Gaming Disorder, included in DSM-5, is precisely the first example of such a diagnosis and will be presented in the next paragraph.

10.3 Internet Gaming Disorder

Children and adolescents play regularly video games, and for the majority of them, this is a harmless habit. However, for a small but significant minority, playing video games can evolve into a problematic condition, akin to a clear addiction. Thus, as Paulus et al. (2018) argue, video gaming can be thought as a continuum from a fun and beneficial activity, to problematic/pathological, to the extreme of addictive use.

Moving from the ample but somewhat inconclusive field of studies regarding Internet Addiction, the American Psychiatric Association, during the development process of DSM-5, opted for including in the third section ("Emerging measures and models") the Internet Gaming Disorder as the one technological addiction with the most solid empirical foundations and evidence for clinical harm. As Petry et al. (2015) highlight, the Substance Use Disorder Workgroup reviewed the potential diagnosis of technological addiction opted to "disentangle the source of access from types of activities that may lead to problems" (p. 2) and thus focused specifically on the gaming function. Moreover, the term "Internet" is meant as a preface to the diagnosis to distinguish it from gambling disorder and to indicate that online gaming is correlated with the higher rate of problems; however, gaming addiction as stated in DMS-5 can be applied to offline play.

Gentile et al. (2017) point out that the aetiology of IGD is still debated and not well understood. It usually implies a consistent amount of time spent playing video games; however, the frequency and duration of gaming are not considered as diagnostic criteria per se. The DSM-5 in fact reports that, as a consequence of video game playing, there must be a clinically significant impairment in the gamer's life. Following APA, the World Health Organization followed up inserting the diagnosis of "Gaming disorder" in the proposed 11th version of the International Classification of Diseases (ICD-11).[2] The diagnosis of Gaming Disorder does not require that the gaming activities occur online, and the criteria are somewhat more inclusive than those of DSM-5. For the diagnostic criteria of Internet Gaming Disorder (DSM-5) and Gaming Addiction (ICD-11), refer to Boxes 10.1 and 10.2.

As regards clusters of symptoms, King et al. (2013) argue that the "core symptoms" of the disorder are withdrawal, loss of control over game use and the conflict with other activities/relevant others of daily life, while other symptoms are considered "peripheral". Charlton and Danforth (2007) similarly indicate in conflict

[2] ICD: International Statistical Classification of Diseases.

Box 10.1 DSM-5 Diagnostic Criteria for Internet Gaming Disorder (APA, 2013)

Persistent and recurrent use of the Internet to engage in games, often with other players, leading to clinically significant impairment or distress as indicated by five (or more) of the following in a 12-month period:

1. Preoccupation with Internet games. (The individual thinks about previous gaming activity or anticipates playing the next game; Internet gaming becomes the dominant activity in daily life).
2. Withdrawal symptoms when Internet gaming is taken away. (These symptoms are typically described as irritability, anxiety, or sadness, but there are no physical signs of pharmacological withdrawal).
3. Tolerance—the need to spend increasing amounts of time engaged in Internet games.
4. Unsuccessful attempts to control the participation in Internet games.
5. Loss of interests in previous hobbies and entertainment as a result of, and with the exception of, Internet games.
6. Continued excessive use of Internet games despite knowledge of psychosocial problems.
7. Has deceived family members, therapists, or others regarding the amount of Internet gaming.
8. Use of Internet games to escape or relieve a negative mood (e.g., feelings of helplessness, guilt, anxiety).
9. Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of participation in Internet games.

Box 10.2 ICD-11 Diagnostic Criteria for Gaming Disorder (WHO, 2018)

Gaming disorder is characterized by a pattern of persistent or recurrent gaming behavior ("digital gaming" or "video-gaming"), which may be online (i.e., over the internet) or offline, manifested by:

1. impaired control over gaming (e.g., onset, frequency, intensity, duration, termination, context);
2. increasing priority given to gaming to the extent that gaming takes precedence over other life interests and daily activities; and
3. continuation or escalation of gaming despite the occurrence of negative consequences.

The pattern of gaming behavior may be continuous or episodic and recurrent. The pattern of gaming behavior results in marked distress or significant impairment in personal, family, social, educational, occupational, or other important areas of functioning. The gaming behavior and other features are normally evident over a period of at least 12 months in order for a diagnosis to be assigned, although the required duration may be shortened if all diagnostic requirements are met and symptoms are severe.

and withdrawal two of the core symptoms, adding relapse and behavioural salience to the lot. Also craving may be considered a potential symptom of IGD (King et al., 2016): Although it is not specifically listed in the diagnostic criteria of DSM-5, it can be thought as a component of withdrawal, and it brings some resemblance with the "Preoccupation" criteria of the diagnosis.

In terms of prevalence, rates vary across countries and age groups. Gentile (2009) reported a prevalence of 8.5% among American gamers aged 8–18, while in Australia, about the 5% of video game players met at least 4 out of 9 criteria of the DSM-5 (Thomas & Martin, 2010). In Europe, rates tend to be lower, and figures include non-gamers: Rehbein et al. (2015) found rates about 1.2% in German youth; Milani et al. (2018) found a prevalence of 2.1% of Italian youth; Lemmens et al. (2015) found a rate of about 5.5% in Netherlands' youth; Tejeiro Salguero and Morán (2002) reported a rate of 9.9% in Spain; Müller et al. (2015) finally computed a global European prevalence rate of 1.6%. Prevalence in Eastern Asian countries seems to be higher, although this result is still debated (cf. Mihara & Higuchi, 2017). Xu and Yuan (2008) reported a prevalence of 21.5% in Chinese adolescents, Chin-Sheng and Chiou (2007) stated a prevalence of 34% and Gentile et al. (2011) found a prevalence of 9% in Singaporean adolescents. This study also showed longitudinally that, over a 2-year period, more than 80% of adolescents that were diagnosed with IGD at the beginning of the research could be classified as still suffering from IGD. Adolescents that retained the diagnosis at the end of the 2-year period showed higher levels of depression and aggression and lower academic grades and worse relations with parents. Also, Mihara and Higuchi (2017) reported a moderate to high stability of IGD symptoms over the course of the disorder.

Petry et al. (2015) report that male gender and younger age appear to be clear demographic risk factors for the onset of IGD, and that some psychological symptoms and disorders appear to be associated with IGD. In particular, social isolation and depression appear to be the most relevant psychosocial risk factors for IGD (Rehbein et al., 2010). Problems of impulsivity and attention deficits have also been correlated with the risk of IGD (Choo et al., 2010). For a more detailed description of risk factors, refer to Sects. 10.4 and 10.5.

In terms of potential maladaptive outcomes and negative consequences, Paulus et al. (2018) show that gaming addicts tend to fare worse in several areas of functioning: education, work, family relations, social relations including romantic partnerships, psychological well-being, sense of the self and self-esteem, and leisure activities. Moreover, there is a potential correlation between gaming addiction and a range of psychiatric disorders (e.g., anxiety, depression, ADHD, obsessive-compulsive disorder, cf. Andreassen et al., 2016). Finally, especially for children and adolescents, IGD can impact academic performance significantly. Farchakh et al. (2020) showed that higher addiction to video gaming was significantly associated with lower academic scores and worse memory performance. The likely explanation is that the interactivity, reward-based progress and the constant perceptual stimulation of video games may habituate students to focus their attention only when presented with highly stimulating environments.

10.4 Risk Factors for the Onset of New Addictions

The mere identification of diagnostic criteria and psychopathological correlates of new addictions is not sufficient to outline the multiple influences these can have on developmental trajectories in youth, and to pinpoint potential risk factors. Thus, scholars dedicated much effort in studying the intertwine of Internet and Gaming Addictions with typical and atypical developmental paths in youth, extending the frame of this field of study beyond diagnosis and comorbidity.

To begin, it may be useful to focus briefly on the motivations of online game play, from the point of view of gamers at risk of addiction. Beranuy et al. (2013) analysed via qualitative interviews the motivations of online game play in a small sample of players seeking treatment for uncontrolled MMORPG[3] play. Results highlight that the main motivations for playing that kind of games are: (a) dissociation (i.e., the possibility to "forget" the present situation and immerse fully in the game); (b) entertainment (i.e., the need to find something to escape the boredom of everyday life) and (c) virtual friendship (i.e., creating relationships through the video game, collaborating with other players). When a player loses control over her/his gaming habits, a conflict arises between these motivations and life "outside" the game, posing serious threats to adjustment.

In terms of psychological adjustment, Lemmens et al. (2011) proposed a comprehensive model for understanding the connection between psychosocial well-being and risk of addiction in youth. Moving from the assumption that psychosocial well-being is of particular importance in adolescence is due for the many developmental challenges faced by youth in that period. The transition between adolescence and young adulthood is in fact characterized by the achievement of milestones such as the consolidation of the in-being adult Self, the formation of romantic relationships, the prospection of professional career and the progressive independence from the family. Thus, low well-being in this age can lead to problems in any of the abovementioned tasks, increasing the risk for difficulties and maladaptive outcomes in a later stage. However, based on previous literature, psychosocial well-being may both be a cause or a consequence of excessive and uncontrolled gaming. If we think about well-being as a consequence, for example, being a video game addict in adolescence can displace those activities that are essential to achieve good adaptation such as maintaining social relationships (Colwell & Kato, 2003). On the contrary, if we think about well-being as a cause, it may be that those adolescents with lower social skills and lower in satisfaction are more at risk of losing control over their playing habits, especially if they use video games as a mean to detach from reality (as shown above) and to seek social relations (Peters & Malesky, 2008). In this light, Lemmens et al. (2011) highlighted that—based on their longitudinal study—well-being can be considered both a precursor *and* a consequence of gaming addiction. In fact, lower social competence, loneliness and a lack of self-esteem were

[3] Massively multiplayer online role-playing game.

predictors of the subsequent risk of addiction. Also, loneliness was a consequence of continued uncontrolled and excessive gaming months later, showing that adolescents that tried to compensate their needs with gaming worsened their feeling of being isolated.

The main areas of study regarding risk factors of IGD/IA and developmental correlates can be grouped into three branches. The first concerns the quality of the social relations of youth at risk of addiction, including relations with parents, teachers and peers, and the related socio-relational dimensions (e.g., social skills, attachment and sense of loneliness). The second branch is related to personal characteristics of youth that engages in problematic use of new technologies, more specifically in terms of personality traits, emotional stability, sensation seeking, etc. … Finally, the third branch focuses on the interplay between maladaptive coping strategies and risk of addiction. We will follow this order to briefly highlight the main findings in the literature in the following sub-paragraphs. In doing so, we will focus mainly on Internet Gaming Disorder, as it is the only technological addiction with a formal set of diagnostic criteria both in ICD-11 (WHO, 2018) and DSM-5 (APA, 2013).

10.4.1 New Addictions and Social Functioning

Earlier studies hypothesized that children and adolescents at risk of IGD could be motivated by the seeking of relationships in an environment perceived as more friendly and controllable than face-to-face interaction. The Social Compensation Hypothesis (Caplan, 2003) posits that lonely individuals are at risk of addictive use of Internet and video games due for their seeking of social opportunities. In doing so, they can engage into a reciprocating circle in which they increment the time spent online for social purposes, actually impoverishing their relations offline.

Subsequent studies that followed this model focused on the correlation between social skills, attachment and use of online games (Kowert & Oldmeadow, 2015), finding positive correlations between insecure attachment and the risk of using video games as a mean to compensate. Authors found that gamers with insecure attachment are more at risk of using games as a mean to regulate their internal state when feeling stressed, anxious or lonely. This is particularly evident for avoidant individuals, leading to conclude that such players seek comfort in the virtual environment as a means to fulfil social needs in a space perceived as "friendly".

Also Škařupová and Blinka (2015) showed that individuals with sub-optimal social functioning (in terms of detachment or overdependence) are more at risk of gaming addiction. On the contrary, gamers with healthy social relations are less at risk of problematic gaming.

Regarding the interplay between attachment and risk of IGD, a study recently showed that the quality of attachment bonds is clearly related to patterns of problematic gaming in youth (Tas, 2019). In particular, avoidant and anxious-ambivalent attachment styles are predictors of the risk of IGD in a sample of preadolescents and adolescents.

Focusing on family factors, Schneider et al. (2017) reviewed the literature with the aim of highlighting the most relevant risk indicators for gaming addiction. The most consistent finding in the review was the weight of the parent–child relation as a potential risk factor of addiction, for the following reasons: (a) gamers at risk of addiction spend less time in social activities with their parents (Jeong & Kim, 2011); (b) addicted gamers tend to report lower levels of affection from their parents if compared with non-addicted gamers (Kwon et al., 2011); and (c) addicted gamers report worse family environment if compared with non-addicted gamers (Da Charlie et al., 2011). Bonnaire and Phan (2017) found that addicted gamers reported more family conflict and less family cohesion than non-addicted gamers, and that the existence of family rules about video game use is correlated with lower risk of addiction. Parental mediation is also related to lower risk of Internet addiction (Chang et al., 2015).

10.4.2 New Addictions and Characteristics of Personality

A second branch of relevant studies on risk factors and correlates of new addictions regards the relation with personality characteristics. These studies focus specifically on the interplay between certain traits (i.e., neuroticism, openness, extraversion, conscientiousness and agreeableness; cf. Costa & McCrae, 1985, 1992) and the risk of addiction in youth. A study by C. Wang et al. (2015a) highlighted the differences in terms of personality traits between Internet addicts, Gaming addicts and Social Network addicts. In line with previous literature on Internet addiction (Yan et al., 2014), they found that high neuroticism and low conscientiousness are related to Internet Addiction, while low conscientiousness and low openness are specifically related to IGD. Finally, Social Network addiction appears to be related to high neuroticism. Also Mehroof and Griffiths (2010) investigated the correlation between IGD and various personality traits, specifically sensation seeking, self-control, aggression, neuroticism, state anxiety and trait anxiety. Their results highlight that the traits mostly associated with IGD are neuroticism, sensation seeking, trait anxiety, state anxiety and aggression.

The correlation between IGD and sensation seeking has been addressed in a recent study by Tian et al. (2019), whose research also targeted the interplay between IGD and the affiliation with deviant peer in adolescence. Their results show that sensation seeking is directly related to the risk of IGD, but that this relation is mediated by the peer influence. Specifically, when adolescents high in sensation seeking partake to deviant peer groups, the risk of IGD is augmented significantly. To counterbalance this dynamic, parental knowledge and monitoring acts as a protective factor: adolescents with high level of parental knowledge have a lower risk of both to affiliate with deviant peers and to incur in IGD.

Another personality-related factor that can counterbalance the risk of IGD in adolescence is the emotional intelligence. Emotional intelligence is a set of abilities that enables individuals to regulate own emotions in relation with environmental

and social cues, while pursuing a sense of well-being. The study from Dang et al. (2019) showed that emotional intelligence (EI) acts as an indirect protective factor against the risk of IGD in a sample of young adults in a 1-year longitudinal study. In particular, it appears that EI can both decrease the risk of psychopathology (i.e., depression) and promote effective coping strategies 1 year later. Consequently, lower psychopathology risk and better coping strategies protect from the risk of addiction.

10.4.3 New Addictions and Coping

The third branch of studies regarding risk factors for technological addictions focuses on the coping strategies in the event of stressful situations. In fact, maladaptive or sub-optimal coping strategies have been identified as potential risk factors for Internet and Gaming addiction since the inception of this field of study.

Coping strategies are defined as the behaviours or cognitions that we use to manage stress when situational or cognitive resources are assessed as insufficient (Lazarus & Folkman, 1984). Families of coping strategies in childhood and adolescence can be roughly summarized into four domains (Skinner & Zimmer-Gembeck, 2007): support seeking, problem solving (or active coping), distraction and avoidance (or escape).

Di Blasi et al. (2019) focused specifically on escapism as a potential risk factor for IGD in a sample of players of MMORPG. Previous literature (Yee, 2006) showed that one of the motivations for engaging in video gaming is to distract from the problems and difficulties of real life and highlighted that escapism can be one of the strongest predictors of IGD, especially in the presence of psychopathology (Ballabio et al., 2017), or problems in emotion regulation (Villani et al., 2018). Di Blasi and colleagues confirmed results of the literature, highlighting that video games are indeed used as a means to cope with negative affects and emotions, reinforcing escapism in the event of stressful situations.

As regards in particular the MMORPG gamers, it appears that recurring to the video game can paradoxically be of some help for those individuals particularly lacking in emotion regulation skills. Maroney et al. (2019) confirmed the role of escapism as a potential risk factor for gaming addiction, acting as a mediator between depression, anxiety and loneliness and gaming habits. In particular, it appears that the game genres interact with the personal disposition of the player: first person shooters (FPS) seem to be particularly apt to provide an escape from negative affects, while MMORPGs may provide socialization opportunities for problematic gamers. Also Moge and Romano (2020) showed that distraction or escape coping can be significant mediators between IGD and the onset of the DAS triad of maladaptive outcomes (Depression, Anxiety and Stress), and in particular that video game addiction is significantly associated with lower active coping and higher avoidance coping.

Bowditch et al. (2018) confirmed a strong correlation between escapism and dysfunctional coping strategies, and both as predictors of technological addictions. Moreover, coping strategies traditionally considered as adaptive (active/problem solving and support seeking) effectively reduce the risk of addiction and operate as protective factors. Schneider et al. (2018) and Milani et al. (2018) identified significant correlations between adolescents' maladaptive coping styles and IGD symptoms, highlighting that this happens both in adolescents with clear IGD and in adolescents with sub-clinical gaming disorder. Melodia et al. (2020), finally, confirmed with a systematic review that escapism and avoidance coping represent general predictors of IGD.

A specific kind of coping which has been correlated with Internet Addiction (cf. Kuss et al., 2017) and IGD (Plante et al., 2019) is media-focused coping. Media-focused coping can be defined as recurring to specific media as a means to regulate emotions, and video games are particularly apt at this thanks to their interactive and captivating characteristics. Plante et al. (2019) showed that young adults with anxiety and that use video games as a "self-treatment" to overcome anxiety are the most at risk of technological addiction, regardless of the time spent video gaming. Also, Lin et al. (2021) found that young adults with media-related dysfunctional coping strategies (in particular venting and self-distraction) are the most at risk of developing gaming addiction. Interestingly, individuals with dysfunctional media-related coping were also at the higher end of perceived stress measures. This clearly shows the circular relation between perceived stress—dysfunctional coping—and addiction, which in turns heightens the stress experienced by the individual.

10.5 New Addictions and Neurobiological Correlates

The research on the link between new addictions and neurophysiological correlates is still in its infancy; however, some results from neurobiological and behavioural research (Frascella et al., 2010) seem to point to the existence of shared vulnerabilities between behavioural addictions and substance abuse (see Chaps. 1 and 2). Early studies showed that the brain activation connected with the impulse for gaming seems to be similar to that of substance abuse (Ko et al., 2009). In particular, cerebral areas activated by the urge of gaming seem to be the anterior cingulate, the orbital frontal lobe, the Nucleus Accumbens, the dorsal striatum and the dorsolateral prefrontal cortex (DLPFC) in addicted gamers (Han et al., 2011; Ko et al., 2009).

According to Volkow et al.'s (2010) model, the vulnerability to addiction is due to anomalies in the information processing and the integration between brain circuits. In particular, the abnormally heightened value given by the subject to addiction-related cues activates reward, motivation and memory circuits with the outcome of overcoming the inhibitory control by the frontal lobe: "*According to this model, in the addicted subject, the saliency value of the drug of abuse and its associated cues is enhanced at the expense of other (natural) rewards, whose saliency is markedly reduced. This would explain the increased motivation to seek the drug.*

However, acute drug exposure also resets reward thresholds, resulting in decreased sensitivity of the reward circuit to reinforcers, which also helps explain the decreasing value of nondrug reinforcers in the addicted person" (Volkow et al., 2010, p. 754).

Ko et al. (2013) confirmed this model in a sample of 30 problematic gamers, 15 in active addiction and 15 in remission, plus 15 controls. Their study involved an fMRI scan to assess the cerebral activation of the subjects with addiction when exposed to game-related cues (screenshots). Results showed that addicted gamers' brain activation in response to gaming cues was higher than that measured in response to neutral cues. Moreover, the activation of addicted gamers was more pronounced than both problematic gamers in remission and controls. Results also highlighted that the most activated cerebral areas in current gaming addicts were the DLPFS and the parahippocampus, showing that these areas may not only be related to craving mechanisms but also with stabilized addiction. The activation of these areas has been previously linked with gambling (Crockford et al., 2005) and with Internet Addiction (Han et al., 2011), confirming the commonality in terms of cerebral processes implicated with different forms of behavioural addiction. A notable result of Ko et al.'s (2013) study is that problematic gamers in remission showed a higher urge to play after being exposed to gaming cues than controls, highlighting the persistence of the salience of gaming-related cues even some time after the cessation of symptoms.

A review by Kuss et al. (2018) has analysed 27 articles that focused upon neurobiological correlates of IGD and implemented these imaging techniques: fMRI, resfMRI, voxel-based morphometry (VBM), positron emission tomography (PET) and EEG. As regards fMRI studies, results confirmed previous literature highlighting the indicating worse response-inhibition and impaired prefrontal cortex functioning in adolescents with IGD (Sun et al., 2014). Results also showed that addicted gamers tend to have decreased visual and auditory functioning (Ding et al., 2014) paired with lower inhibitory control (Luijten et al., 2015). The resting state fMRI (resfMRI) studies showed that addicted gamers tend to have impaired cognitive control (Lin et al., 2015a) and reward system (Lin et al., 2015b). More specifically, these studies have shown that individuals with IGD tend to have decreased white matter density in the inferior frontal gyrus, insula, amygdala and anterior cingulate, all probable underpinnings of the decreased abilities in regulating behaviour of addicted gamers. Studies using VBM point out the existence of grey matter anomalies in addicted gamers, especially in those areas linked with executive control (supplementary motor area and anterior cingulate cortex; Lee et al., 2018) and with impulsivity (especially right dorsomedial prefrontal cortex and amygdala; Du et al., 2016). Moreover, the research with voxel-based morphometry seems to concur on the potential harmful effects of IGD on grey matter, as shown by Y. Wang et al. (2015b) and Brand et al. (2014). Results of PET studies focus on the activation of dopamine-sensible areas of the brain during gameplay and show that using a video game can activate the dopaminergic system in a similar way of substances (cf. Koepp et al., 1998; Park et al., 2010). Apparently, addicted gamers tend to show alterations in the striatum as an outcome of excessive video game play (Tian et al.,

2014). Finally, EEG studies point out that addicted gamers tend to show ERPs compatible with sub-optimal error-processing in Go/NoGo tasks and lower inhibitory control if compared to controls (Littel et al., 2012), and a lower activation of the reward-related P300 if compared to controls, leading to attribute this atypical response to tolerance (Duven et al., 2015). Park, Choi et al. (2016b) further substantiated this evidence showing that gamers with IGD are characterized by sub-optimal information processing, attested by attenuated P300 amplitude to novel stimuli in an oddball task. Mostly interesting, the severity of IGD was negatively correlated with the amplitude of P300, showing the impact of gaming addiction upon superior cerebral functions. The alterations of EEG of IGD gamers were reported also in resting state scans, particularly in Delta and Theta bands, highlighting long-term alterations likely produced by the disorder (Kim et al., 2017).

10.6 Treatment

Given the relevance of the proposed disorders and the impact in terms of developmental outcomes, literature started to focus on the treatment options and programmes available in the field. At the moment, the treatment of Internet-related disorders, especially IGD, is still considered at "experimental stage" and characterized by methodological lack of standards (cf. Peter et al., 2020).

The literature seems to converge on the Cognitive Behavioural Therapy (CBT) as the most promising form of treatment of technological addiction (Griffiths et al., 2016a; King et al., 2011; Petry, 2019; Pontes et al., 2015; Winkler et al., 2013), while some authors consider useful pair cognitive-behavioural therapy with medication (cf. Przepiórka et al., 2014). As Griffiths et al. (2016a) point out that usually the treatment is set up in stages, focusing firstly on the behavioural aspects of the addiction and moving towards cognitive functioning later on. In this light, the importance of coping strategies, as previously highlighted, becomes evident. The final goal of treatment usually aims to empower the gamer with the ability to identify the situational and psychological triggers that promote addictive gaming.

Therapists working with addicted patients usually note that they are similar in certain regards to substance addicts, namely the use of the medium to modulate the mood, the salience of the activity, the tolerance, the conflict with other daily activities and the withdrawal symptoms (cf. Kuss & Griffiths, 2015).

A review by Kuss and Lopez-Fernandez (2016) focused on the treatment of Internet Addiction (including problematic Internet use) and Internet Gaming Disorder, providing a useful reference about both kinds of technological addiction. Their main terms of inclusion in the review were: (a) containing quantitative empirical data; (b) having been published after 2000 and (c) including clinical samples and/or clinical interventions for Internet and/or gaming addiction. A total of 152 studies were found in the first stage of the inquiry, with 46 of them fully meeting the inclusion criteria. Authors aggregated the 46 studies selected into four main type of contribution: (a) research involving treatment seeker characteristics; (b) studies

about psychopharmacotherapy; (c) psychological therapy and (d) combined treatment.

As concerns the characteristics of the individuals seeking treatment for IA or IGD, the range of age was comprised between 16 and 30.5 years old, with a vast majority of males over females. Patients seeking treatment for Internet Addiction were diagnosed with a comorbidity of some sort, in particular: 14% had a comorbid ADHD, 7% had hypomania, 15% had a generalized anxiety disorder, 15% had a social anxiety disorder, 7% were dysthymic, 7% had an obsessive-compulsive personality disorder, 14% had a borderline personality disorder, 7% had an avoidant personality disorder and 2% had a binge eating disorder. Patients that required treatment for Internet Gaming Disorder were characterized by the following comorbidities: 40% had antisocial personality traits, 56.7% had effective disorders (30% major depression and 26.7% dysthymia), 26.7% had other addictions and 16.7% had antisocial disorders. Moreover, if compared with controls, individuals suffering from IGD or IA were characterized by higher scores of depression and anxiety, recurred to maladaptive coping strategies and had lower scores of global functioning and social competence.

Regarding the studies about pharmacotherapy, Kuss and Lopez-Fernandez (2016) reported a study on a single case (Atmaca, 2007) that was successfully treated with a combination of selective serotonin reuptake inhibitors (SSRI) and antipsychotic medication, leading to a symptom remission that was still evident on a 4-month follow-up. Another study replicated the use of SSRI in the treatment of Internet Addiction and Internet Gaming Disorder with apparently good results: Dell'Osso et al. (2008) found that the antidepressant was effective in reducing uncontrolled Internet use in the patient group. In terms of antidepressant use, the study of Han et al. (2009) highlighted that the use of antidepressant was able to reduce craving and diminish the time spent playing and the brain activity related to the stimulus. Overall, it seems that the use of antidepressant is the therapy of choice for the treatment of Internet/Gaming addiction, possibly due to the comorbidity of these with mood disorders.

In terms of psychological treatment, Kuss and Lopez-Fernandez (2016) highlighted that most of the research reported data about CBT, with duration of treatment comprised between weeks (Du et al., 2010) and a few months (Wölfling et al., 2014). Generally, the main aims of psychological treatment are to gain control over the activities on the Internet, ameliorating the coping strategies of the patients, improving the quality of the communication with others and increasing the ability to manage the media. The treatment programmes often include group sessions that can comprise also the family of the patient (Liu et al., 2015) and peer-support groups (Shek et al., 2009). As regards the effectiveness of the psychological treatment alone, research shows some inconclusive results as some studies failed to find differences between treatment group and control group especially when the treatment is individual (Du et al., 2010; Ge et al., 2011). On the contrary, approaches using CBT group sessions seem to obtain better results (Kim, 2008; Liu et al., 2015).

According to Kuss and Lopez-Fernandez (2016), finally, combined therapy seems to be a promising form of treatment for IGD and IA. Combined therapy is

characterized by psychological treatment in association with either pharmacotherapy, another form of psychological intervention (e.g., motivational interventions, life skills education) or electroacupuncture. Their review highlights that the combined therapies were effective in reducing the symptoms of Internet-related problems.

A review by Zajac et al. (2017) specifically differentiated between treatment of IGD and Internet Addiction, and excluded smaller studies and case reports due to their lack of statistical power regarding the effectiveness of the treatment. The selection process led to analyse 26 studies with rigorous multiarmed procedure and/or pre-test and post-test evidence. Thirteen of the studies were focused on Internet Gaming Disorder and 13 on Internet Addiction.

As regards specifically IGD, five of the studies selected were focused on pharmacotherapy, four on CBT treatment and the remaining four were aimed at other types of intervention. Studies on pharmacotherapy examined medications usually aimed at treating ADHD or depression, and found a significant decrease in IGD symptoms following a treatment with bupropion (Han et al., 2011; Song et al., 2016) or following a treatment with either atomoxetine or methylphenidate (Park, Lee et al., 2016a). The four studies on CBT on the whole highlighted a certain effectiveness in reducing IGD symptomatology in young adults (Zhang et al., 2016) and adolescents (Li & Wang, 2013), and indicated that CBT plus medication (bupropion) was more effective than medication alone (Kim et al., 2012). The four studies on other treatment were focused on: (a) family therapy, which was effective in decreasing IGD symptoms (Han et al., 2012); (b) a mix of eclectic psychotherapy, family therapy and motivational interviewing, which led to unclear results as parents reported a decrease in IGD symptoms but patients did not (Pallesen et al., 2015); (c) a residential camp experience for adolescents, including CBT and personal counselling, which led to a stable decrease of IGD symptoms (Sakuma et al., 2017); (d) an educational programme aimed at speaking and writing skills, which proved to decrease the time of gaming (Kim et al., 2013). Overall, the results of the review led Zajac et al. (2017) to evaluate the treatments as still "Experimental" (for guidelines, refer to Chambless et al., 1996).

Peter et al. (2020) focused specifically on IGD and identified five key points that any treatment addressing this disorder should encompass: (a) monitoring of the time spent gaming; (b) taking into consideration the patterns of gaming in the different moments of the day; (c) setting limits on the daily time of gaming; (d) providing a set of pleasurable activities as a substitute for gaming and (e) involving other people to support the patient in monitoring his/her gaming and engaging in substitute activities. Monitoring time spent gaming is a key task in early phases of treatment, to provide both a measure of progress in treatment and a means to gain knowledge about the relevance of the problem to the patient. Moreover, as shown in previous paragraphs, the amount of game play during night time or times of the day spent into productive activities (i.e., school or work) is usually associated with higher scores of addiction (cf. Triberti et al., 2018). Monitoring time spent gaming can provide the therapist with valuable information about the patterns of behaviour of the patient and help set goals for the treatment. For example, a patient may increase

his or her playing time on specific occasions (e.g., when stressed, bored or angry) or in response to specific needs (e.g., to remain connected with friends using a specific video game). Setting limits about gaming may be a useful strategy to help the patient and should comprise the option of not pursuing the complete abstinence. The reason for opting to limit and not to stop gaming is due to the potential positive outcomes of controlled gaming, especially for patient with comorbidities (e.g., gaming may be a temporary way of escaping symptoms of depression). The therapist should also help the patient to identify a set of pleasurable activities she or he could engage into instead of gaming. This can be accomplished, for example, asking the patient to think what activities were most engaging for her/his prior to the onset of the IGD. In doing so, the therapist should make sure that the patient (a) is able to actually engage into those activities and (b) at least some of them include social opportunities. As seen in the previous paragraphs, in fact, given the importance of gaming as a means of socialization, reducing gaming time may also reduce social opportunities for patients. Finally, the therapist should integrate parents and/or supportive others in the treatment, as a further motivation for change and as a support in terms of accountability and recognition of the efforts made by the patient in reducing gaming time and regaining control over sessions of play.

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