SISSA
Scuola
Internazionale
Superiore di
Studi Avanzati

Neuroscience Area – PhD course in

Cognitive Neuroscience

Too much, too little. Understanding the mechanisms underlying disorders of excessive and diminished motivation.

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Academic Year 2018-19

Der suchende.

INDEX

OVERVIEW

Motivation is a complex process essential for the survival of individuals that produces behaviors in response to the changing of internal and environmental conditions (Salamone et al., 2016; Simpson and Balsam, 2016). A key variable influencing motivation is the availability of rewards. Indeed, in everyday life, rewards motivate behavior and provide enjoyment, favoring adaptation and health functioning. However, motivated behavior can get disrupted, leading to different pathological misdirection of motivation including apathy, anhedonia and impulse control disorders (ICD). Therefore, the aim of the present thesis is to investigate processes, such as reward responsiveness (reward liking and wanting) and reward valuation (temporal and effort discounting of rewards), that have been considered as likely contributors of abnormal motivation across neurological and psychiatric disorders. All these aspects are introduced in Chapter 1 of my thesis, while in the following Chapters (2-3) I will report original studies in which I used different techniques to explore disorders of excessive (Chapter 2) and diminished (Chapter 3) motivation.

In Study 1, reward responsiveness was investigated in Parkinson's disease (PD) patients with binge eating (BE) by asking them to perform different experimental tasks assessing food liking and wanting (Chapter 2). The results of this study showed that BE in PD was associated with cognitive abnormalities, and to lesser extent affective abnormalities, but not with an increased wanting of rewards.

In Study 2 I tested the hypothesis that PD patients with different impulse control disorders (ICD) may have altered reward responsiveness and reward valuation, and that the DLPFC may have a causal role in such alterations. In this study transcranial direct current stimulation (tDCS) over DLPFC was used when PD patients with and without ICD and healthy matched controls performed a reward responsiveness task employing explicit (self-ratings of liking and wanting) and implicit (heart beat and skin conductance response) measures, and two temporal discounting tasks in order to measure their reward valuation processes. Results showed that patients with ICD and PD have a greater liking

and wanting of rewards, as well as a steeper temporal discounting of rewards compared to controls. Moreover, tDCS may be capable to modulate the altered intensity of PD+ICD patients' liking, but not their altered wanting and temporal discounting of rewards.

In Study 3 I investigated whether deficits in reward valuation, commonly reported in schizophrenia, can be observed also in individuals with subclinical psychotic symptoms (PS) to determine if this dysfunction is already present in a potentially pre-psychotic period (Chapter 3). Participants with different levels of subclinical psychotic symptoms (PS) performed effort and temporal discounting tasks. Results showed that aberrant and effort cost computations might be present in individuals with high levels of subclinical PS.

In Study 4 I aimed to replicate previous findings of Study 3 and to investigate the neuroimaging correlates, using electroencephalography (EEG), of this abnormal reward valuation in individuals with high levels of PS (Chapter 3). We confirmed that individuals with high PS exhibit altered temporal discounting of rewards relative to individuals with low PS. However, differently from Study 3, high PS participants did not show a greater effort discounting of rewards. Interestingly, even if no differences emerged at a behavioral level, we observed an higher sensitivity to the cost of effort in individuals with high PS (indexed via the LFA, an electrophysiological measure of motivation), but not in those with low PS.

In the final chapter I discussed the main findings obtained in my studies in the light of the extant literature (Chapter 4).

CHAPTER 1

General Introduction

Motivation is a complex and fundamental component of human behavior. One of the first attempt to explain motivation was the *drive reduction theory* proposed by the psychologist Hull (1943), according to which, motivation is a way for the organism to restore balance and meet its needs. Subsequently, Hebb (1949) argued that motivation is a "stimulation that arouses activity of a particular kind". Importantly, this conceptualization of motivation that included both an arousal component and a goal-directed component has inspired more recent developments that emphasize its dual role to satisfying basic needs (such as food or social interaction) and pursuing goals (Robinson and Berridge, 1993; Simpson and Balsam, 2016; Koob, 2015).

Notably, motivation can be influenced by different factors, including physiological states and environmental conditions (Daw and Shohami, 2008; Koob, 2015). Among them, a key variable is the availability of rewards. A *reward* is as an object that has an appetitive value that can increase the motivation to engage in a particular behavior (Kim, 2013). The value of a reward can be phylogenetically determined in the case of primary rewards (e.g., food or sex) or can be learned through classical or instrumental learning in the case of secondary rewards (e.g., money), in which neutral stimuli become "rewarding" (Berridge, 2004; Di Chiara, 2005; Sescousse et al., 2013). As follows, rewards can influence motivated behavior by eliciting behavioral reactions such as approach and consumption (Berridge, 2004; Niv et al., 2006).

In everyday life, rewards motivate behavior and provide enjoyment, favoring adaptation and health functioning (Berridge, 2004, 2007; Kim, 2016). However, motivated behavior can get disrupted, leading to different pathological misdirection of motivation including apathy, anhedonia and impulse control disorders. This chapter focuses on processes that have been considered as likely contributors of abnormal motivation across neurological and psychiatric disorders, such as reward responsiveness (reward liking and wanting) and reward valuation (effort and temporal discounting of

rewards). Studies on impaired reward response and evaluation can help us in better understanding facets of motivational behaviors.

1.1 Dopamine and the regulation of motivated behavior

Motivation is a complex process mediated by different and interactive neural circuits. It is known that dopamine (DA) neuron systems play a critical role in different facets of motivation, in addition to many other essential functions such as the control of movements, emotion, and cognition. While early studies in the 1970s have mainly empathized the role of this neurotransmitter in the control of movements (Bernheimer et al., 1973; Rolls et al., 1974), subsequent studies in the 1980s and the 1990s began to extend the role of DA also to the domain of motivation (Mogenson et al., 1980; Alheid and Heimer, 1988; Heimer et al., 1991; Salamone, 1994). In particular, pharmacology and lesion studies in rats showed that DA can be involved in motivated behavior by using effort-based decision-making tasks (see next paragraph for further details on these tasks). For example, DA antagonists (e.g., neuroleptic drugs) seem to reduce the willingness to work for more preferred or larger rewards without affecting motor or learning abilities (Cousins and Salamone, 1994; Salamone et al., 2007). In contrast, DA agonists (e.g., d-amphetamine drugs) lead to the opposite result, suggesting an increased willingness to work for rewards. Crucially, the overall consumption of rewards and the hedonic reactions were still intact following either DA antagonists and agonists manipulations (Bardget et al., 2009; Salamone and Correa, 2002; Salamone et al., 2016).

Research on the neuroanatomical substrates of motivation showed that mesolimbic DA neurons project to motor but also to limbic and frontal areas, usually associated with motivation and cognition (see Di Chiara, 2005 for a review). These early observations in rats led to suggest that the majority of DA neurons in humans resides in the mesencephalon and are located in three major nuclei: the substantia nigra pars compacta (SNpc), the ventral tegmental area (VTA), and the retrorubral field (Björklund and Lindvall, 1984; Björklund and Dunnet, 2007). DA neurons in the SNpc transmit DA

to the dorsal striatum (caudate nucleus and putamen) via the nigrostriatal pathway, while DA neurons in the VTA project mainly to the nucleus accumbens (via the mesolimbic pathway) and the prefrontal (PFC), cingulate and perirhinal cortex (via the mesocortical pathway) (Wise et al., 2004; Arias-Carrión and Pöppel, 2007) (Figure 1.1). Importantly, it has been proposed that mesolimbic and mesocortical pathways, usually referred to as the mesocorticolimbic pathway, play a key role in motivated behavior (Berridge and Robinson, 1998; Salamone et al., 2016). Indeed, this system has also been defined as the "Dopamine Motive System" (Volkow et al., 2017).

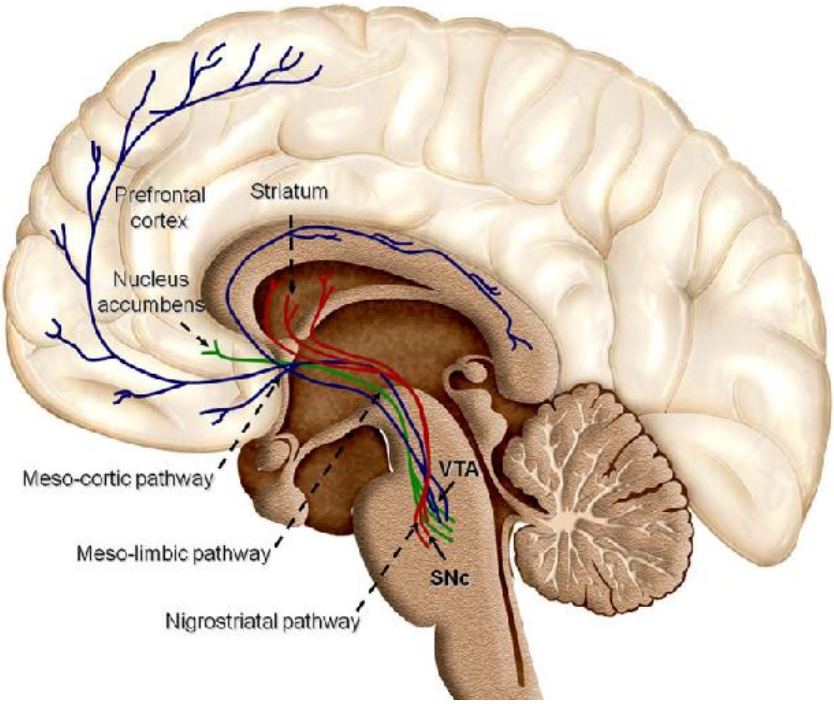

Figure 1.1 Dopamine pathways. Depicted are projections from VTA to the NAc (mesolimbic pathway), and PFC (mesocortical pathway); and projections from the SN to the dorsal striautum (nigrostriatal pathway). Adapted from Arias-Carrión and Pöppel (2007).

However, different hypotheses regarding the functional properties of the mesocorticolimbic DA system have been proposed but a general agreement has not been reached to date (Wise, 2002). While according to Wise (1985) the DA mediates the hedonic value of a stimulus, for Schultz it is involved in learning through prediction error signals (Schultz et al., 1997). Furthermore, the DA has been proposed to be involved in incentive motivation and to play a role in reward anticipation (also known as "wanting") (the Incentive Salience hypothesis, Berridge and Robinson, 1998; 2003). Yet

other accounts have suggested that the DA system represents both a motivational signal and a learning signal (see Volkow et al., 2017; Berke, 2018). Accordingly, tonic DA activity of midbrain neurons (slow DA changes) is critical for motivation, while phasic DA activity (fast DA changes) mediates learning. In line with this view, tonic DA activity signals expected events and determines motivational arousal. In contrast, phasic DA activity signals positive or negative reward-prediction error if these events are better or worse than expected. In other words, mesolimbic DA neurons are involved in the processing of motivationally relevant events and the magnitude of DA level determines the sensitivity of the animal to these events (or motivational arousal) (see Volkow et al., 2017).

In sum, the DA system has been found to be involved in several processes including reinforcement learning and incentive salience of reward. In particular, the role of this system in reward anticipation could be critical in motivated behavior. However, how DA is involved in linking reward with motivation is still not well known and further research is needed (Berke, 2018).

1.2 Quantifying motivation

Précis

There is ample evidence that motivation is related to the ability to anticipate rewards and to evaluate the costs involved in obtaining them. Accordingly, two main components of motivation can be distinguished: a reward-driven component and a value-based one (Schultz et al. 2005; Kim, 2013). In line with this view, the Research Domain Criteria (RDoC, Cuthbert and Insel, 2013) proposed by the National Institute of Mental Health's Research (NIMH) suggests that these components are comprises into the "positive valence system". On the one hand, this system mediates *reward responsiveness*, including the anticipation of rewards (or "wanting") and the receipt of rewards (or "liking"), on the other hand, it allows the *evaluation of the rewards*, including the computations required to integrate reward value and its related costs (e.g., uncertainty, time, effort). Given the centrality of reward responsiveness and reward valuation in psychopathology (Barch et al., 2016;

Husain et al., 2018; Le Heron et al., 2019), studies providing evidences for impairments in these constructs in individuals with neurological and psychiatric disorders may be critical to understanding facets of their functional impairments.

Reward responsiveness: Liking versus Wanting

The neural circuits mediating the motivation to approach a reward can be dissociated from those responsible for the hedonic pleasure of reward. In the context of motivational research, the *Incentive Salience hypothesis* proposed by Robinson and Berridge (1998) posits that the brain has one system responsible for hedonic pleasure (or "liking"), and one independent but interconnected system, responsible for "wanting" a reward (or incentive salience). These "liking" and "wanting" systems (with quotation marks) refer to the implicit core hedonic pleasure and the visceral and unconscious desire for reward, respectively. Liking (without quotation marks) refers to the explicit subjective and conscious experience of pleasure. Similarly, wanting (without quotation marks) indicates a conscious, explicit cognitive desire (Berridge, 2004; Berridge and Kringelbach, 2015).

The attempt to disentangle between these two components of reward is derived from studies on drug addiction. Specifically, Berridge and Robinson (1993) posited that addiction is characterized by an excessive amplification of the motivation to get the drug ("wanting"), especially triggered by cues, without necessarily an increased pleasure derived from consuming it ("liking"). In line with this early observation, several subsequent studies have shown that "liking" and "wanting" are mediated by different neural systems and that DA has a critical role in modulating "wanting" but not "liking" (Robinson et al., 2005). Thus, even if we usually want things that we like (and the opposite), it is possible to selectively manipulate one of the two systems without affecting the other. For example, using orofacial expression (e.g., rhythmic tongue protrusion or licking the lips) as an objective measure of "liking" sweet tastes, studies on rats have shown that disruption of DA eliminates "wanting" to eat but leaves unimpaired rats' sweetness "liking" (Berridge et al., 1989, Cannon and

Palmiter, 2003; Berridge, 2018). Conversely, enhancing DA levels in mesocorticolimbic circuits through electric stimulation (Berridge and Valenstein, 1991) or genetic manipulation (Pecina et al., 2003) increases "wanting" to eat but still without affecting the pleasure (or "liking") derived from eating. Similar results have been found for the "liking" component: it is possible to increase or decrease "liking" by stimulating or inhibiting hedonic "hot-spots" in the brain, without affecting the "wanting" system (Castro and Berridge, 2014).

Interestingly, a substantial body of human research seems to confirm the "liking"/"wanting" distinction observed in animals (Berridge et al., 2018). For example, DA blockade through DA antagonists decreases self-report wanting or behavioral consumption of addictive drugs (e.g., amphetamine), but has no effect on self-report liking (Wachtel et al. 2002; Leyton, 2010). Similarly, higher DA levels correlate with greater subjective ratings of wanting but not liking in positron emission tomography (PET) (O'Sullivan et al., 2011) and fMRI studies (Politis et al., 2013, Voon et al., 2011). However, it should be mentioned that several studies employing both explicit measures (self-reports) and behavioral implicit measures, such as the Implicit Association Test (IAT, Greenwald et al., 1998), the Approach-Avoidance Task (AAT, Chen and Bargh, 1999), and the Affective Simon Task (AST, De Houwer et al., 1998) failed to confirm the independence of liking and wanting (Pool et al., 2016; Havermans, 2011, 2012; Tibboel et al., 2015). One difficulty in human research is the operationalization of liking and wanting constructs (Pool et al., 2016). As previously mentioned, explicit wanting (or cognitive desire) which relies on higher cognitive functions and is involved in goal-directed behavior (Berridge et al., 1998), is a more complex variable which may involve past hedonic memories (or "expected pleasantness") (Pool et al., 2016). Furthermore, behavioral implicit tasks may be far from the implicit "liking" and "wanting" investigated in animal studies.

As regards the neurochemical and neuroanatomical basis of liking and wanting in animals, the above mentioned studies have suggested that "wanting" can be increased by stimulating any part of the mesolimbic system. Thus, "wanting" is generated by larger and distributed neural substrates

relative to the anatomically small and functionally fragile neural substrates of "liking". Conversely, "liking" appears to be mediated by other neurotransmitters such as opioid and endocannabinoid (Berridge and Kringelbach, 2015) and its neural substrates are represented by small hedonic "hot spots" within greater mesolimbic structures (Smith and Berridge, 2007).

Studies with humans showed that, while wanting is mediated by the activity of different areas of the reward circuit such as the VS, orbitofrontal cortex (OFC), prelimbic cortex and insular cortex (Berridge, 2009; O'Doherty et al., 2001; O'Doherty, 2004; Kringelbach, 2005), the brain regions involved in human liking include subcortical areas such as the ventral tegmental area (VTA), hypothalamus, periventricular grey/periacqueductal grey (PVG/PAG), NAc, ventral pallidum and amygdala; as well as cortical areas including OFC and cingulate and insular cortices (Kringelbach, 2009; Berridge and Kringelbach, 2015) (see Figure 1.2).

To sum up, multiple research strands, involving either rodents and humans, suggest that liking and wanting are distinct component, and that DA modulates wanting but not liking. In addition, wanting rather than liking plays a critical role in motivated behavior. However, the distinction between these two neuro-psychological processes in humans and their relationship with motivated behavior remain an important issue that requires further investigation, particularly with implicit measures (Pool et al., 2016). Moreover, since motivation is a complex process, the function of DA neurons is not limited to direct behavior toward rewarding stimuli but it has also different roles. For example, another complementary hypothesis is that DA mesocorticolimbic pathway is involved in effort-related choices (Salamone et al., 2007; 2016) (see next paragraph).

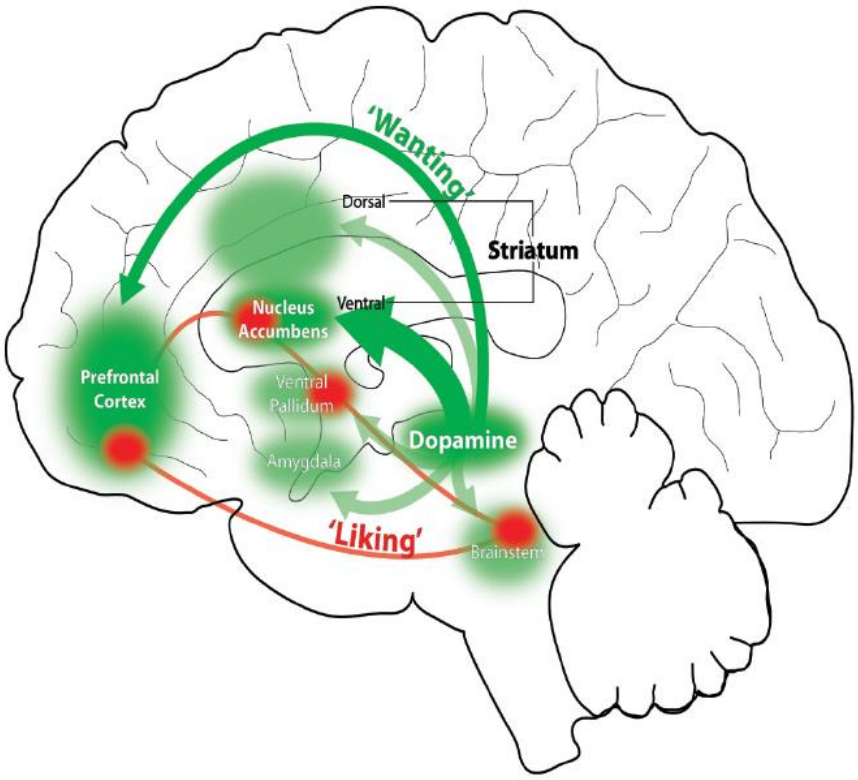

Figure 1.2 Neural substrates of Wanting versus Liking. Larger and distributed mesocorticolimbic substrate of wanting (green) relative to the anatomically small and functionally fragile neural substrate of liking (red). Adapted from Berridge (2018).

Reward valuation: effort cost decision making and effort discounting of rewards

Motivation is a fundamental component to obtain rewards and it is influenced by the evaluation of the costs to obtain them. Different costs may be associated with the behavioral action, including physical and mental effort, time (see next paragraph), probability and danger. Particularly, in the present paragraph, I will discuss the behavioral and neural correlates of cost-benefit computations involved in effort-based decision making.

Pursuing benefits requires to weigh the amount of effort we are willing to exert in order to obtain a reward. This process of evaluation is incorporated in the worth that a person places on a good, or the *subjective value* of the reward (Kable and Glimcher, 2007; Padoa-Schioppa, 2011; Zald and Treadway, 2017). Different studies in humans have quantified motivation through effort-based

decision-making paradigms, both in health and disease. These paradigms attempt to objectively assess motivation by measuring how much effort one individual is willing to exert for different magnitudes of reward. Effort decision making tasks are grounded in a substantial body of research in nonhuman animals (Salamone et al., 2016; Pardo et al., 2012), and are based on two main assumptions. First, higher levels of motivation facilitate to overcome the cost of effort required to obtain rewards (and the opposite). Second, the net value of a reward is higher if it does not require effort to obtain it, and is lower if it does (Kivetz, 2003; Phillips et al., 2007; Salamone et al., 2016; Rudebeck et al., 2006). Thus, the subjective value of a reward decreases as the effort required to obtain it increases. This principle is known as *effort discounting* of rewards (Botvinick et al., 2009).

Two main types of effort have been investigated in the literature: physical and cognitive (Hosking et al., 2015; Chong et al., 2017). Physical effort-based decision making can be explored through different experimental approaches, mainly derived from animal studies (Figure 1.3) in which rats are typically asked to make a decision between a more preferred reward and a less preferred one or between a larger reward and a small reward. However, the first option can be obtained only by exerting a certain amount of physical effort while the second is freely available. For example, in a T-maze choice task rats are asked to climb a barrier in one arm for a larger reward, whereas no barrier is present in the arm of the small reward (Salamone et al., 1994; Izquierdo and Belcher, 2012). Similarly, a progressive ratio schedule paradigm requires to progressively increase the effort (i.e., number of lever presses) to obtain the more preferred/larger reward while holding constant the effort for the less preferred/small reward. In human studies the physical effort has been operationalized as the amount of force exerted on a hand-held dynamometer for different magnitudes of reward (Chong et al., 2015; Bonnelle et al., 2016; Prévost et al., 2010) or as the amount of button presses on the keyboard (Treadway et al., 2009; Giesen et al., 2010; Porat et al. 2014).

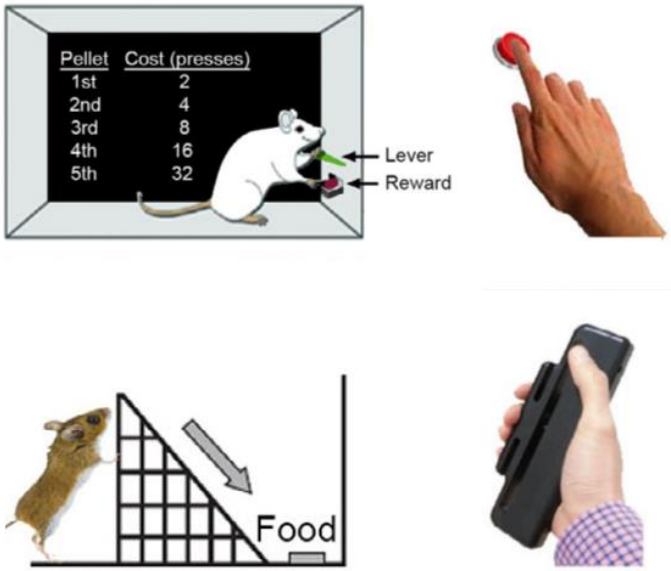

Figure 1.3 Physical effort. Effort manipulations in terms of the number of lever presses in getting a reward, or, in humans, as the number of button presses (top); effort manipulations based on the steepness of a barrier to overcome in pursuing of a reward, or, in humans, as the amount of force applied to a hand-held dynamometer (bottom). Adapted from Chong et al. (2016).

In addition to the physical domain, obtaining a reward may require also a certain degree of cognitive demand (Westbrook and Braver, 2015). Particularly, the decision to expend cognitive effort can be assessed through cognitive effort discounting tasks (e.g., using an n-back task), in which participants are asked to choose between a low effort option (in terms of cognitive load) for smaller rewards and a high effort option for larger rewards. Interestingly, it has been shown that rats avoid large rewards when cognitive effort is required during a visuospatial attention task (Hosking et al., 2014, 2015). However, studies investigating cognitive effort-based decision making in animals are rare due to the difficulty to train animals to perform cognitive tasks (Chong et al., 2016). Cognitive effort in human studies has been manipulated through visuospatial attention tasks (Apps et al., 2015), but also by the demands of working memory (Westbrook et al., 2013), task switching (Kool et al., 2010), perceptual (Reddy et al., 2015) and conflict (Schmidt et al., 2012) tasks.

In order to measure how subjective value of rewards decays as the cost of effort increases, several computational modeling approaches have been proposed. However, differently from the well-documented mathematical models proposed for describing temporal discounting of rewards (see next

paragraph), computational models of effort discounting are surprisingly understudied and only recently there has been a growing interest on them (Bialaszek et al., 2017). Each model has a different prediction of how subjective value is devalued as a function of effort. For example, a linear model that predicts how subjective value is discounted in a constant way as effort increases, has been mainly suggested for progressive ratio tasks in which a persistent effort over time is required (e.g., through lever/button presses) (Chong et al., 2016). Differently, a hyperbolic model predicts a higher discounting for change in the effort at lower relative to higher levels, whereas a parabolic model predicts the opposite (Chong et al., 2016, 2018). Interestingly, it has been proposed that effort costs devalue rewards in a parabolic way (in contrast with the delay costs; see next paragraph), which means small devaluations for lower efforts, and larger devaluations for higher efforts levels (Klein-Flügge et al., 2015).

Moreover, neuroscientists have begun employing effort discounting tasks also in neuroimaging studies in order to explore the neural correlates of motivation. Different brain areas have been reported to be involved in effort-based decision making including the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (dlPFC), anterior insula (AI), amygdala and nucleus accumbens (NAcc). Specifically, it has been proposed that the dACC sends information about effort demands to the NAcc, setting up a sort of "reference point" for measuring reward on the basis of the cost of the effort to obtain it (Botvinick et al., 2009; Rushworth et al., 2004; Walton et al., 2006). Once this process has been computed, corticostriatal connections linking ACC to the NAcc are supposed to transform this strategy into the appropriate behavioral output (Floresco et al., 1999; Parkinson et al., 2000). The NAcc has indeed been found to be less activated following a high-demand effort condition compared to a low-demand one and the activation of ACC (in particular its dorsal region, dACC) to correlate with the magnitude of the effect found in the NAcc (Botvinick et al., 2009). Moreover, since reduced connectivity between ACC and SMA is associated with lower levels of motivation (Kurniawan et al., 2013, Zénon et al., 2015), it has also been suggested that this network

may play a critical role in weighing the cost of effort in the decision-making process (Bonnelle et al., 2016).

However, other studies have suggested that ACC encodes not only whether a specific action is worth performing but also its discounting effect on the subjective value of the reward (Prévost et al., 2010), since ACC negatively correlates with the subjective value of effortful reward during effort discounting tasks (Prévost et al., 2010; Croxon et al., 2009). Rewards devaluations by effort may be subserved also by the network mPFC-dlPFC, typically associated with higher-level cognitive processes such as working memory and goal maintenance (Miller and Cohen, 2001). This network may have a role in the expectation of effortful control, showing higher activity as a function of task difficulty (Vassena et al., 2017; Chong et al., 2017).

Interestingly, the involvement of the above-mentioned brain areas seems to be shared by both physical and cognitive effort (Nishiyama, 2016). However, in one study in which cognitive and physical effort have been compared, the amygdala seemed to play a specific role in processing the value of rewards associated only with cognitive effort (Chong et al., 2016). Similar findings have been reported in rodents (Hosking et al., 2014), suggesting a domain-specificity of the amygdala in cognitive effort valuation (Chong et al., 2016, 2017).

In conclusion, effort is an important factor influencing motivated behavior. The growing interest in effort-discounting paradigms during the last years has had the advance to better quantify the underlying mechanisms of motivation. However, further research is needed in order to understand the computational and neural bases of effort-based decision making in healthy and pathological individuals.

Reward valuation: temporal cost decision making and temporal discounting of rewards

Rewards associated with the cost of effort are devalued in a similar way to those associated with the cost of time. Therefore, another important factor in determining decision making is the time of the occurrence of rewards (Frederik et al., 2002).

Usually, our decisions imply future consequences. For example, choices about diet, retirement, and smoking may have long-term effects on people's life. The ability to evaluate effects delayed in time is a key factor of decision making (Kable, 2013), and it is fundamental for decisions known as *intertemporal choices*, which are indicative of *delay* or *temporal discounting* (TD, Samuelson, 1937; Ainslie, 1974). This term refers to the established phenomenon according to which passage of time reduces the subjective value of a reward (Green and Myerson, 2004; Kable and Glimcher, 2007). Interestingly, different studies have found that humans and other animals tend to prefer immediate rewards over delayed ones of equal magnitude, even if the first option implies a smaller amount of rewards (Ainslie et al., 1974; Rosati et al., 2007). Thus, in line with the TD account, the choice of the smaller/immediate amount of rewards is due to a devaluation of the larger/delayed one (Frederick et al., 2002; Kable, 2013).

Usually, in TD tasks in humans these two alternatives are arranged side by side on the computer screen and participants make their decisions by pressing one of two buttons on the keyboard or by using the cursor of a computer mouse (see Figure 1.4).

Figure 1.4 Example trial sequence of a TD task. Participants chose between a smaller/immediate amount of reward and a larger/delayed amount of reward. Adapted from Sellitto et al., 2010.

These tasks allow measuring both reaction time of the choice and subjective value of the reward for different delays by using specific adjustment procedures (Reynold and Schiffbauer, 2004; da Matta et al., 2012). In particular, the amount of reward during each trial of a TD task can be adjusted based on the participant's choice made in the previous one. For example, if the participant chooses the immediate option, then the amount of reward for this option in the following trial will decrease (and the opposite). According to a commonly used staircase procedure for TD tasks, the size of the adjustment for the first trial of each delay block corresponds to half of the difference between the immediate and delayed reward, and for subsequent trials it's half of the difference of the previous adjustment (Du et al., 2002; Myerson et al., 2003; Sellitto et al., 2010).

An alternative to computerized TD task is the Kirby Delay-Discounting Questionnaire (Kirby et al., 1999), consisting in a series of 27 questions about smaller/immediate rewards and larger/delayed ones. However, since time intervals in this questionnaire are fewer than those usually employed in the majority of studies with computerized TD tasks, this tool has shown a lower sensitivity (especially with small amounts) (Epstein et al., 2003; da Matta et al., 2014).

Several studies have investigated the mathematical relationships among reward magnitude, delay, and subjective value. For example, early theoretical works in economics proposed that the subjective value of the reward is discounted exponentially as a function of time (Samuelson, 1937). The assumption of this exponential decay function is that it follows a constant discount rate, which means that people apply the same discount rate at each delay. However, animal and human research has suggested that the discount rate may not be constant but can be approximately hyperbolic (Ainslie, 1992). Specifically, hyperbolic discounting functions predict that the rate of discounting decreases for further future delays. Thus, the choice of smaller but immediate rewards instead of larger but delayed ones occurs more for near future and less for distant future (Mazur, 1987; Ainslie, 1975). This model has been found to give a better description of human TD compared to the exponential model (Green et al., 1997). Furthermore, a hyperbolic discount of rewards has been found also in eye-

tracking studies in which the cost of the action was operationalized as the duration and the velocity of saccades (Shadmer et al., 2010; Haith et al., 2012). Interestingly, midbrain DA neurons of the monkey also discharge in a hyperbolic form in response to cues predicting future reward. Thus, the response of these neurons to the cue predicting the shortest time delay (near future) is strong, while the response for cues predicting a longer time delay (distant future) decays hyperbolically (Kobayashi and Schultz, 2008).

Hyperbolic and exponential models are based on theoretical assumptions related to the parameters of the discounting functions and there is still a lack of theoretical agreement in the literature (Myerson et al., 2001; da Matta et al., 2012). In addition, fitting an exponential or hyperbolic model to the data can generate asymmetric distribution and heterogeneous variance (Myerson et al., 2001). An alternative or complementary measure frequently computed in studies on TD is the calculation of the area under the curve (AUC, Myerson et al., 2001). This measure is a model-free parameter since it is not based on theoretical assumptions. Furthermore, this approach avoids the aforementioned quantitative analysis problems of model fitting (Ohmura et al., 2006).

Cognitive neuroscientists began to investigate the neural correlates of TD. For example, McClure and colleagues showed that two systems may be engaged in TD tasks. One "impetuous" limbic system involving midbrain DA neurons (particularly in the VS) and paralimbic cortex (including mOFC and mPFC) is associated with choices for immediate rewards. One "provident" system involving the lateral PFC and posterior parietal cortex (PPC) is engaged for both immediate and delayed choices (McClure et al., 2004). Based on this evidence, it has been proposed that impulsivity may result from an imbalance between the two systems (McClure et al., 2004, 2007). In contrast, others failed to report a greater activation of VS, mPFC and PCC for the choice of immediate reward compared to the choice of the delayed one (Kable and Glimcher, 2007, 2010; Frost and McNaughton, 2017). It has been proposed that these regions might not be responding to immediacy *per se* but to the larger subjective value of immediate rewards (Levy and Glimcher, 2012; Kable, 2013). Many subsequent studies have supported the conclusion that a unitary system involving

several regions, rather than a dual system, encodes the subjective value of both immediate and delayed rewards (Ranghel and Hare, 2010; Peters and Buchel, 2009, 2010). Specifically a growing number of neuroimaging studies has shown the fundamental role of VS and vmPFC in computing the subjective value of immediate and delayed rewards during intertemporal choices (Glimcher, 2009; Levy and Glimcher, 2012; Kable, 2013). Patients with mOFC lesions, within the vmPFC, showed a steeper TD, suggesting the critical role of this area for valuation and preferences of delayed rewards (Sellitto et al., 2010). In line with the idea that vmPFC plays a critical role in intertemporal choices, it has been proposed that the activity of this area encodes the overall subjective value of the reward (Hare et al., 2009). In addition, the interaction between lateral PFC and vmPFC may bias behavior towards larger/delayed rewards (Hare et al., 2009; Frost and McNaughton, 2017; Kable, 2013).

In sum, intertemporal choices are crucial in decision making and the discounting rate is an important contributor to self-control. Indeed, steeper TD is associated with impulsive behavior. Furthermore, recent neuroimaging and lesions studies suggest that a unitary system involving several regions, such as VS and vmPFC, respond to both immediate and delayed rewards, and that brain activity in these areas reflects individuals' TD rates.

1.3 Motivational disorders: focus on Parkinson's disease and Schizophrenia

Précis

Motivation is a complex process essential for the survival of individuals that produces behaviors in response to the changing of internal and environmental conditions (Salamone et al., 2016; Simpson and Balsam, 2016). Consequently, deficits in motivation are important determinants of functional disability, with devastating consequences for people's life (Epstein et al., 2015; Voon et al., 2017). Motivational deficits occur in both psychiatric and neurological conditions and have been distinguished into two main categories: disorders of excessive and diminished motivation (Simpson

et al., 2016; Voon et al., 2011; Zald et al., 2017). The first category is represented by disorders of excessive misdirection of motivation, including excessive goal-related activity, urgency, and impulsivity (commonly observed in impulse control disorders and addiction). Conversely, the second category includes apathy, anhedonia, avolition, depression and negative symptoms (commonly observed in schizophrenia) (Epstein et al., 2015; Zald et al., 2017). According to the RDoC model (Cuthbert and Insel, 2013) proposed by the NIMH, deficits in reward-related processes may represent a core source for different motivational disorders and are linked to alterations in brain DA and related circuits (Volkow et al., 2017; Voon et al., 2011, 2017). Thus, apathy and depression from one side and impulse control disorders (ICDs) from the other side could represent two different ends of a behavioral DA-dependent continuum (Figure 1.5) and result associated with a lower (hypodopaminergic state) and a higher (hyperdopaminergic state) DA function, respectively (Voon et al., 2011, 2017).

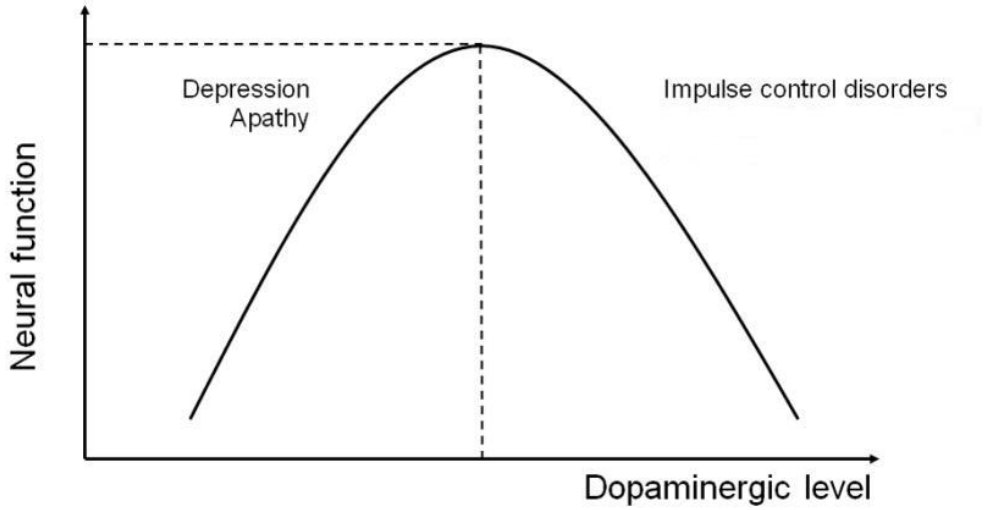

Figure 1.5 Dopamine level, neural function and behavior. Efficient neural/behavioral function follows a "inverted-U" shape function with both higher and lower dopamine levels associated with impaired function, while a midrange level is associated with optimal function. Adapted from Voon et al. (2011).

Recent studies have suggested that investigating reward responsiveness (e.g., liking and wanting) and reward valuation (e.g., effort/temporal based decision making) may contribute to understanding the neurobehavioral processes that underlie motivational disorders (Reddy et al., 2016;

Epstein et al. 2015; Husain et al., 2018). In the following paragraphs, I will review the literature on these components of motivational disorders, with a particular focus on ICDs in Parkinson's disease (PD, as an example of excessive motivation) and negative symptoms in schizophrenia (as an example of diminished motivation).

Excessive motivation: Impulse Control Disorders in Parkinson's disease

Parkinson's disease (PD) is a movement disorder, affecting approximately 2–3% of the population ≥ 65 years of age. It is also characterized by many non-motor symptoms such as cognitive deficits and mood disturbances, which have a profound impact on the quality of life of patients (Poewe et al., 2017; Vriend et al., 2014; Voon et al., 2017). These symptoms comprise pathological and repetitive behaviors such as gambling, compulsive shopping, sexual behaviors, binge eating, compulsive use of dopaminergic medications and punding (Voon et al., 2017; Antonini et al., 2017). They are defined as "the inability to resist an impulse, drive, or temptation to perform an act that is harmful to the person or others" (American Psychiatric Association, 2000), and occur in about 17% of patients on dopaminergic medication (Voon et al., 2017). Several risk factors have been associated with their development in PD, including age (≤65 years), being unmarried, a family history of gambling problems and ongoing cigarette smoking (Weintraub et al., 2010). However, it has been shown that the greatest risk factor for developing ICDs is the use of dopaminergic medications (Weintraub et al., 2010; Voon et al., 2017). Indeed, with regards to the pathophysiology of ICDs in PD, the DA "overdose" hypothesis (Weintraub et al., 2008; Napier et al., 2015) posits that prolonged exposure to DA replacement therapies may explain their phenomenology. Particularly, since in PD ventral striatal dopamine is preserved relative to dorsal striatal activity (Cools, 2006; Weintraub et al., 2008), it is believed that dopaminergic treatment used to alleviate motor dorsal striatal deficiencies may result in an "over-dosing" in ventral cortico-striatal cognitive and limbic pathways (Voon et al., 2011, 2017; Weintraub et al., 2008; Napier et al., 2015).

Consistently, several studies have found an enhanced incentive salience attribution (or "wanting") to rewards in patients with ICDs (see Voon et al., 2017 and Antonini et al., 2017 for a review). For example, it has been shown (see Figure 1.6) that presenting rewarding cues to PD patients with ICDs (compared with those without ICDs) is associated with a greater ventral striatal DA release in PET studies (O'Sullivan et al., 2011; Evans et al., 2006; Steeves et al., 2009; Cilia et al., 2010), and a greater activity in the VS in fMRI studies (Politis et al., 2013; Frosini et al., 2010; Vriend, 2018). Furthermore, consistently with the Incentive Salience Hypothesis (Berridge and Robinson, 2009), it has been found that "wanting" but not "liking" ratings in these patients significantly correlates with the activity in the VS (Figure 1.6; Evans et al., 2006; Steeves et al., 2009; Politis et al., 2013).

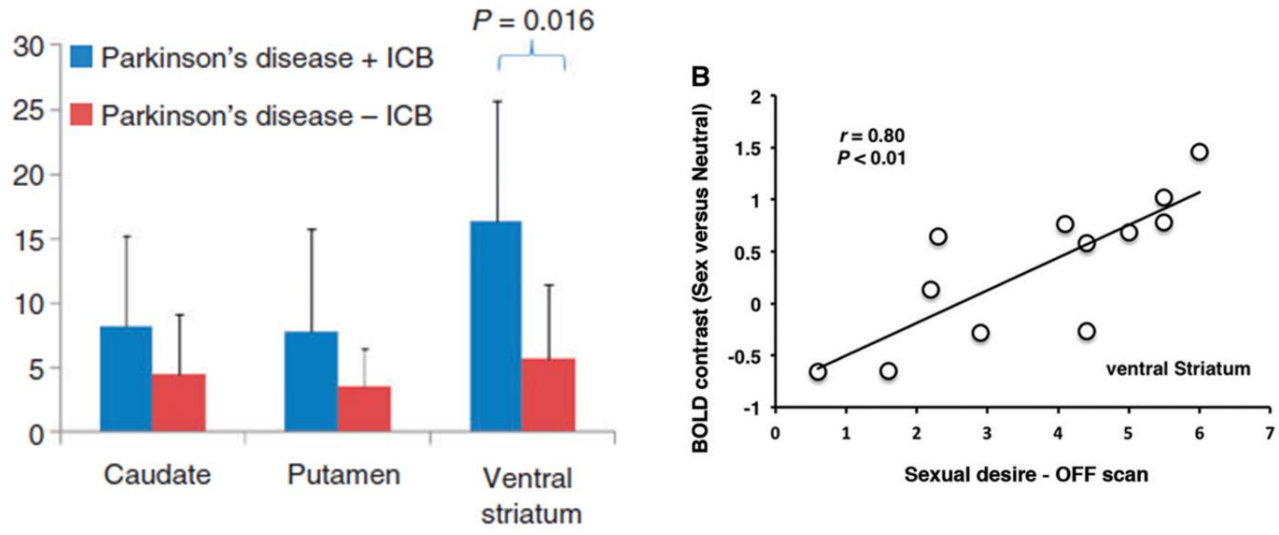

Figure 1.6 (Left) Reduction in ^{11}C-raclopride binding potential (mean percentage) in PD patients with and without ICDs following the presentation of reward-related cues; error bars represent standard deviation. Adapted from O'Sullivan et al. (2011). (Right) Positive correlation between the activity contrast in the VS (sex versus neutral) of PD patients with hypersexuality and their sexual desire ("wanting") post-exposure to sexual visual cues. Adapted from Politis et al. (2013).

Other studies have reported that ICDs are not only associated with alterations in reward responsiveness but also with reward valuation (see Santangelo et al., 2017 for a review), suggesting an alteration of decision-making processes too (Napier et al. 2015; Voon et al., 2011; Housden et al., 2010). For instance, in TD tasks, PD-ICDs patients consistently showed a preference for the

smaller/immediate amount of reward over the larger/delayed one with either hypothetical or real rewards (see Figure 1.7, Voon et al., 2011; Housden et al., 2010). This aberrant TD is mainly driven by an inability to wait for the larger/delayed reward rather than over-valuation of the small/immediate reward (Housden et al., 2010). Furthermore, the higher devaluation of larger/delayed rewards has been associated with dopamine agonists (Napier et al., 2015). Similar results have been found in *probability discounting task*, showing that dopamine agonists are associate with an increased risk taking in PD-ICDs patients (Djamshidian et al., 2013; Voon et al., 2011). As to the effort-based decision making, it has been shown that DA increases willingness to exert effort in PD patients tested in ON and OFF medication (Chong et al., 2015, 2016), but no studies have to date compared PD-ICDs patients with those without ICDs or healthy controls. Finally, cognitive deficits, which may affect decision making processes, have been documented in PD-ICDs patients such as working memory deficits, dysfunction of abstraction ability, set-shifting and visuospatial/constructional abilities (Santangelo et al., 2017).

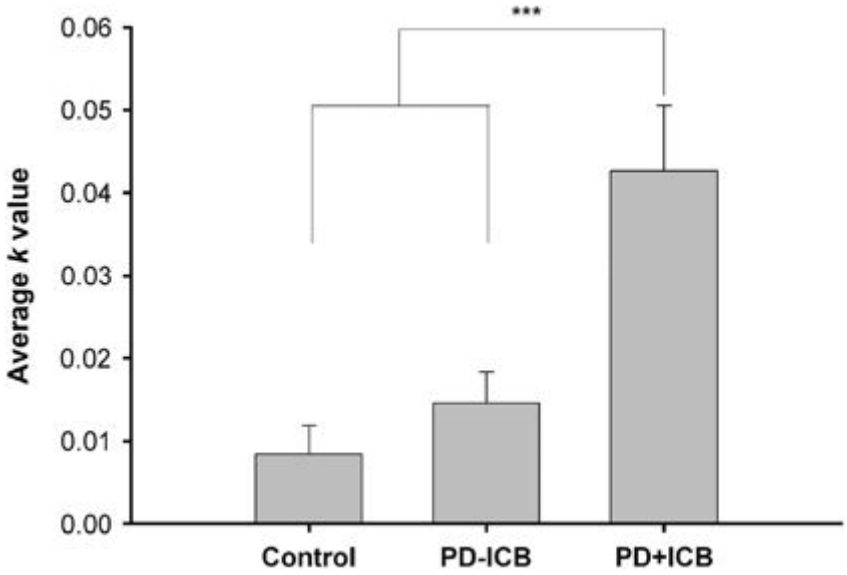

Figure 1.7 Hyperbolic discounting measure (*k*). PD patients with ICDs showed a steeper TD relative to PD patients without ICDs and healthy controls, who did not differ. Values are means; error bars represent standard error. $^{***}p<0.001$. Adapted from Housden et al. (2010).

Neuroimaging studies have confirmed the involvement of both reward responsiveness and reward valuation networks in Parkinson patients with ICDs. Both PET and fMRI studies have linked the presence of ICDs to an alteration of different brain regions in frontostriatal networks such as the prefrontal cortex (PFC), the orbitofrontal cortex (OFC), the cingulate cortex and the striatum (O'Sullivan et al., 2011; Steeves et al., 2009; Cilia et al., 2011; vanEimeren et al., 2010; Voon et al., 2010; Politis et al., 2013). Patterns of atrophy in these regions have also been reported in morphometric studies (Pellicano et al., 2015; Biundo et al., 2015).

In conclusion, during the past decade research has provided impressive advances not only in the diagnosis of ICDs but also in understanding their neuroanatomical substrates through neuroimaging studies (Napier et al., 2015). Results suggest that ICDs in PD are characterized by higher levels of reward responsiveness, particularly in the wanting component, which may reflect sensitization of reward-related areas such as the VS. Furthermore, they suggest also alterations of reward valuation processes by showing higher impulsivity in ICDs patients when performing TD tasks. Future studies should also investigate also effort-based decision making in PD-ICDs patients. In addition, larger sample size studies are needed in order to address not only similarities but also differences among ICDs (Voon et al., 2011, 2017).

Diminished motivation: negative symptoms in Schizophrenia

Schizophrenia is a chronic, psychotic mental disorder that affects about 1% of humans (van Os and Kapur, 2009). Symptoms of schizophrenia have been clustered into four dimensions: positive symptoms (e.g., hallucinations and delusions), negative symptoms (affective flattening, alogia, avolition, social withdrawal and anhedonia), depressive symptoms and cognitive impairment (Kay et al., 1987; van Os and Kapur, 2009; Tandon et al., 2013). In recent years, interest in motivational disturbances of patients with schizophrenia has grown as they lead to functional disability, and several

studies have linked motivational disturbances to the subdomain of negative symptoms and in particular to anhedonia (see Reddy et al., 2016 for a review).

Anhedonia is defined as the decreased response to pleasurable stimuli (Frost and Strauss, 2016; Gard et al., 2007). Up to 80% of patients with schizophrenia show at least moderate levels of anhedonia (Fonseca-Pedrero et al., 2014) and this symptom has been recognized as the most influential factor associated with the poor social, educational and vocational achievement in these patients (Lee et al., 2015; Thomsen, 2015). It has been suggested that anhedonia may affect two separate constructs of reward responsiveness: the anticipation (wanting) and the experience (liking) of pleasure (Thomsen et al., 2015). The presence of deficits of these processes in schizophrenia has been studied mainly with the Temporal Experience of Pleasure Scale (TEPS), a short questionnaire developed by Gard (Gard et al., 2007). Using the TEPS, studies have shown that patients with schizophrenia have deficits in anticipatory, but not in consummatory pleasure (Gard et al., 2007; Wynn et al., 2010; Mote et al., 2014) even if other evidence suggested otherwise (Tremeau et al., 2010, 2014; Gard et al., 2014).

Neuroimaging experiments of reward responsiveness in schizophrenia have provided similar results by measuring neural responses to reward-predicting cue mostly with Monetary Incentive Delay Tasks (Knutson et al., 2001). In these studies medicated (Juckel et al., 2006; Simon et al., 2015; Schlagenhauf et al., 2009) and drug-naïve unmedicated schizophrenia patients (Juckel et al., 2012; Wotruba et al., 2014), showed decreased ventral striatal activation during anticipatory pleasure, while consummatory pleasure resulted intact. Furthermore, anticipatory pleasure resulted associated with anhedonia (see Figure 1.8) assessed with the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987), a validated questionnaire for measuring positive and negative symptoms in schizophrenia.

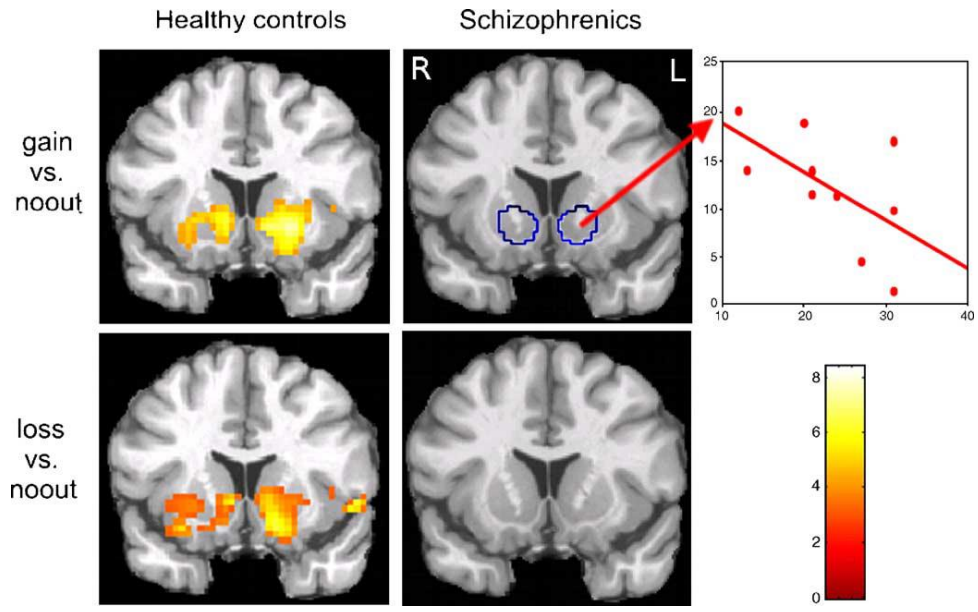

Figure 1.8 Activity of the VS during anticipation of gain and loss in healthy controls and unmedicated schizophrenics. Significant activations of the VS (bilaterally) of healthy controls during the presentation of reward cues and loss cues (versus no-outcome cues). No significant activations for both contrasts in the VS of schizophrenics, in which also low activation of the left VS by reward cues was correlated with increased severity of negative symptoms. Adapted from Juckel et al. (2006).

It has been hypothesized that a high striatal DA turnover may increase the "noise" in the reward system, thus interfering with the neuronal processing of reward-predicting cues by phasic DA release. This, in turn, may contribute to negative symptoms such as anhedonia (Juckel et al., 2006; Goldstein and Volkow, 2002).

As to the role of reward valuation processes in motivational deficits in schizophrenia, the willingness to exert effort for rewards is another index that has been the subject of recent studies (Figure 1.9). It has been found that these patients are less willing to work to obtain rewards (Fervaha et al., 2013; Treadway et al., 2015). Furthermore, the devaluation of rewards associated with effort has been found to correlate with the severity of negative symptoms, in particular, avolition and anhedonia (Gold et al., 2013; Gold and Frank, 2015; Hartmann et al., 2015). Similar results have been found in temporal discounting studies (see Figure 1.9). In particular, impulsive reward valuation has been observed in patients with schizophrenia by showing a steeper discounting of monetary rewards compared to controls (Ahn et al., 2011; Brown et al., 2018; Yu et al., 2017). Higher temporal

discounting rates have also been found to correlate with the severity of negative symptoms: the steeper the discounting the more severe were the negative symptoms (Heerey et al., 2007, 2011).

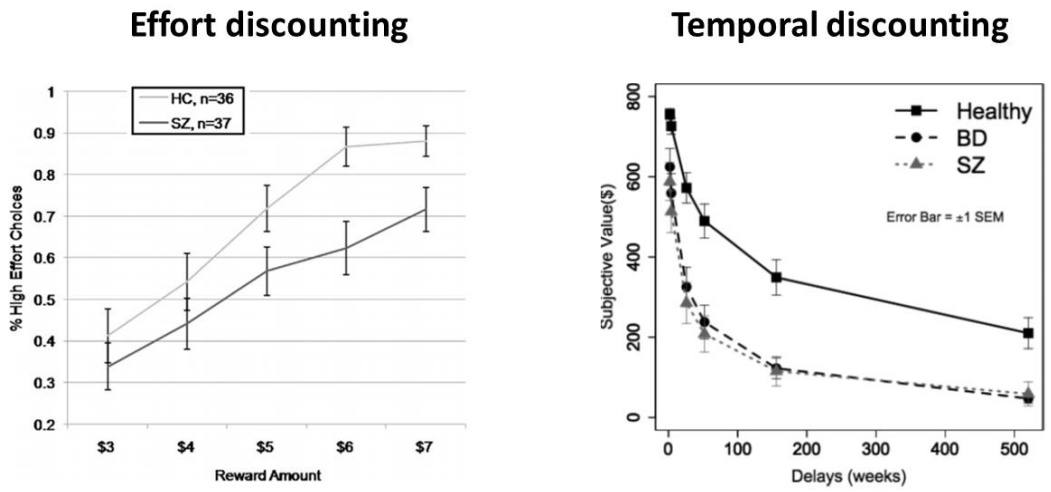

Figure 1.9 (Left) Effort discounting. Proportion of effort choices as a function of reward amount for each group. SZ: Schizophrenia; HC: healthy controls; adapted from Gold et al. (2015). (Right) Temporal discounting. Mean subjective value of rewards as a function of the delay for each group. BD: Bipolar Disorder, SZ: Schizophrenia; adapted from Ahn et al. (2011)

Overall, these alterations have been associated with functional abnormalities in brain reward-related regions such as OFC and/or ACC (Gold et al., 2012, 2013). Patterns of atrophy in these regions have also been reported in morphometric studies (Kawasaki et al., 2004; Honea et al., 2005; Brugger and Howes, 2017).

Taken together, these studies suggest that negative symptoms are important contributors to motivational deficits in schizophrenia, which include altered reward responsiveness (reduced anticipatory pleasure) and altered reward valuation (steeper effort and temporal discounting of rewards).

CHAPTER 2

Excessive motivation: Impulse Control Disorders in Parkinson's Disease

Study 1

Reward sensitivity in Parkinson's patients with binge eating

[This study has been published in Terenzi et al., 2018]

Abstract

Parkinson's disease (PD) patients who are treated with dopamine replacement therapy are at risk of developing impulse control disorders (ICDs) (such as gambling, binge eating, and others). According to recent evidence, compulsive reward seeking in ICDs may arise from an excessive attribution of incentive salience (or 'wanting') to rewards.

In this study, we tested this hypothesis in patients with PD who developed binge eating (BE). Patients with BE, patients without BE, and healthy controls performed different experimental tasks assessing food liking and wanting. Participants first rated the degree of liking and wanting for different foods using explicit self-report measures. They then performed an affective priming task that measured participants' affective reactions towards foods (liking), and a grip-force task that assessed their motivation for food rewards (wanting). All participants also completed several questionnaires assessing impulsivity, reward sensitivity, anxiety and depression, and underwent a neuropsychological evaluation.

Patients with BE displayed an altered liking for sweet foods compared to controls but not to patients without BE. Furthermore, this difference emerged only when implicit measures were used. Importantly, an increased wanting was not associated with binge eating even if wanting, but not liking scores significantly correlated with LED levodopa, confirming the hypothesis of a distinction between

the two components of rewards. Lastly, binge eating was associated with depression and lower working memory scores.

Take together these results suggest that binge eating in PD is associated with cognitive abnormalities, and to lesser extent affective abnormalities, but not with an increased incentive salience

2.1 Introduction

Parkinson's disease (PD) patients who are treated with dopaminergic medications are at risk of developing impulse control disorders (ICDs), which include pathological and repetitive behaviors such as gambling, compulsive shopping, sexual behaviors, binge eating, compulsive use of dopaminergic medications and punding (Voon et al., 2017). These disorders occur with percentages varying from 3.5% to 42.8% and they are believed to reflect the interaction of dopaminergic treatments (dopamine agonists and/or dopamine replacement therapy) with the individual's susceptibility and the underlying neurobiology of PD (Cossu et al., 2017; Antonini et al., 2017).

Several fMRI and PET studies support the hypothesis that ICDs, like addictive disorders, may be characterized by an excessive attribution of "incentive salience" (or 'wanting') to rewards. These studies have shown an increased activity in different reward brain regions after reward presentation in PD patients with ICDs compared to control patients (O'Sullivan et al., 2011; Evans et al., 2006; Steeves et al., 2009; Politis et al., 2013), and that 'wanting' but not 'liking' ratings in these patients significantly correlate with the activity in the ventral striatum (Evans et al., 2006; Steeves et al., 2009). Even in behavioral tasks, ICDs patients have also shown to exhibit an increased willingness to work for a reward compared to patients without ICDs (Evans et al., 2006). These findings are in line with the incentive sensitization theory, according to which the degree of 'wanting' for a reward increases disproportionately compared to the degree of which the reward is liked as patients develop an addictive disorder. Liking and wanting are indeed considered as separate reward components,

mediating, respectively, the pleasure effect of a reward and the motivational drive toward it (Berridge et al., 2009).

Among ICDs, binge eating (BE) is described as recurrent episodes of increased eating coupled with a perceived lack of control (American Psychiatric Association, 2000). It occurs in 4.3% of PD patients taking dopaminergic medications, it is more common in women (Weintraub et al., 2010; Evans et al., 2009), and it is often associated with increased body weight (Nirenberg et al., 2006). In binge eater patients without PD, this disorder has been related to the mechanisms implicated in addictive disorders, including elevated motivation to seek out palatable foods, greater neural activation in reward related circuitry to high-calorie foods, and impairment in cognitive control (Balodis et al., 2013). However, to date the hypothesis of an enhanced incentive salience attribution to reward in ICDs has never been tested in patients with BE.

To fill this gap, PD patients with BE, PD patients without BE and healthy controls performed several tasks assessing food liking and wanting. First, in order to measure the patients' conscious and subjective experience of food rewards, we had them rate the degree of “liking” and “wanting” for different foods using explicit self-reports. Second, participants performed an affective priming task that measures attitude and affective reactions towards foods, and a grip-force task, in which motivation towards rewards was indirectly operationalized as the exerted effort. Participants also underwent a series of neuropsychological tests and completed several questionnaires evaluating impulsivity, reward sensitivity and the presence of anxiety and depression.

2.2 Methods

Subjects

Thirty-one dopaminergic treated patients with PD and twenty healthy controls (C) took part in the study. PD patients were recruited from the movement disorders clinic of “Cattinara” hospital

in Trieste (Italy). Patients were assessed by a neurologist and asked to fill the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) (Weintraub et al., 2012). Since no validation on the Italian population is available, we used a translated version of the questionnaire. Sixteen PD participants were identified as binge eaters (PD + BE), with ten exhibiting at least one additional ICDs (see Appendix A, Table S2.1). The other fifteen PD patients (PD) had no history of BE or other ICDs. Patients' disease severity was assessed using the Unified Parkinson's Disease Rating Scale-Part III (UPDRS-III) and the Hoehn and Yahr scale (H&Y) (Hoehn and Yahr, 1967). In addition, for each patient a daily L-dopa equivalent dose (LED total) was calculated based on (Tomlinson et al., 2010). The study was approved by SISSA Ethics Committee and all participants provided written informed consent. For details on demographical and clinical data, see Table 2.1.

Experimental Evaluation

We collected participant's subjective ratings of hunger and fasting in order to control for macroscopic differences between subjects. We collected participants' weight and height, and calculated body mass index (BMI) by dividing weight in kilograms by the square of height in meters (kg/m^2). Participants were then asked to perform the experimental tasks, undergo a neuropsychological examination and complete several questionnaires.

Self-ratings of "liking" and "wanting" for foods

In this task, 20 food pictures were presented and participants were asked to respond to the questions: (1) "How tasty is this food for you?" (Liking) and (2) "How much do you want this food now"? (Wanting). The experimenter indicated patients' responses on a 100 visual analogue scale anchored at each end with "not at all" and "extremely" (Aiello et al., 2017). In addition, participants were also asked the question: "How often do you eat this food?" Foods normally not eaten (Frequency: 0e10) were removed from the analysis. On average 9.35% of food items were removed for each patient.

Liking: affective priming task

Participants were instructed that they would see a picture (prime), followed by a smiley symbol (target), and that their task was to indicate whether the smiley was a positive or negative one, by pressing the marked keys (see Papies et al., 2009). Participants were instructed to not pay attention to prime stimuli and to respond as quickly and accurately as possible. The prime stimuli were 20 food pictures and 10 food-unrelated filler pictures (e.g., a comb, a hanger, a wardrobe, etc.) used as filler. The target stimuli were a positive and a negative emoticon (☺ and ☹).

The allocation of responses (positive/negative) to the response buttons was counterbalanced among participants. RTs on trials with errors or RTs below and above 2SD were excluded from the analyses. Each trial consisted of 250 ms prime period, a blank screen of 50 ms, resulting in a stimulus onset asynchrony (SOA) of a 300 ms, a target (which remained on screen until a response was given), and an intertrial interval period of 1500 ms. Each of the prime was presented twice (once followed by the negative target and once followed by the positive one), resulting in 60 trials. In order to determine participants' attitude, a positivity index was constructed for each item type by subtracting from the RTs for negative emotions the RTs for positive emoticons. Thus, lower values of this index indicate a more negative attitude. Stimulus presentation and data collection were accomplished using the Eprime software installed on a desktop computer.

Wanting: grip-force task

Participants were instructed that they would see reward pictures and that their task was to squeeze the handgrip proportionally to how much they want the stimuli (see Van Koningsbruggen et al., 2012). The stimuli were pictures depicting primary rewards (foods) and, as a control condition, secondary rewards (six different amounts of euro coins: 1cent-1 euro). Every trial began with a fixation point (+) for 5000 ms, followed by the picture of the reward for 3500 ms. The inter-trial interval was 5000 ms. All trials were presented in a random order. There were two blocks of 13 trials each. Prior to the task, we collected a baseline measure for the hand dynamometer and the participant's

maximal effort (MVC) (Ziaudden et al., 2014). This procedure was used to control for individual differences in strength. To analyze handgrip-force, we extracted in every trial the maximum or peak force exerted, which was expressed as a percentage of the MVC. Stimulus presentation was programmed on a PC using Psychopy v1.8, connected to a hand dynamometer of a Biopac™ system measuring handgrip-force.

Stimuli

The visual stimuli used were high-quality 20 colored photographs depicting food items and 10 photographs depicting food unrelated items. More in detail, we selected 10 sweet and 10 salty food items, among those more frequently consumed by an independent sample of PD patients (Aiello et al., 2017). The same 20 food visual stimuli were used in each of the three experimental tasks. Sweet and salty foods were matched according to their frequency of consumption and tastiness.

Clinical and neuropsychological evaluation

All participants filled the Barratt Impulsiveness Scale (BIS-11), the Behavioral Inhibition & Activation Scales (BIS/BAS), and the Hospital Anxiety and Depression Scale (HADS). In addition, participants completed Mini Mental State Examination (MMSE), Frontal Assessment Battery (FAB), Semantic Verbal Fluency test, Trail Making Test (TMT), Attentive Matrices, Digit Span Forward, Rey's 15-word test and Poppelreuter-Ghent Test.

Statistical analysis

Data were analyzed using Statistica 7.0 (StatSoft, USA) software. Parametric and non-parametric tests were used where appropriate. Shapiro-Wilk test was undertaken to demonstrate that data were normally distributed. More in detail, for demographic, clinical, questionnaire and neuropsychological measures, comparisons between groups (e.g., PD+BE vs PD, PD+BE vs C, and

PD vs C) were performed using independent samples t tests or Mann-Whitney U test. Gender distribution was analyzed using $_X^2$ test.

Self-ratings of "liking", "wanting" and grip-force task were analyzed using repeated-measures analyses of variance (ANOVA). For self-ratings, food (sweet/salty) was the within-subjects variable. For grip-force task, reward (sweet-foods/salty-foods/money) was the within-subjects variable. Group (PD+BE/PD/C) was the between-subjects variable in all analyses. For the affective priming task, comparisons between groups were performed using Mann-Whitney U test. Spearman's rho correlation was used to examine the relationship between demographic, clinical, questionnaire, neuropsychological and behavioral measures.

2.3 Results

Demographic and clinical data

PD+BE, PD and C were matched for gender, age and education. Importantly, PD+BE had a significantly higher BMI compared to PD and C (see **Appendix A**). Finally, PD+BE, PD and C participants did not significantly differ on subjective ratings of hunger and fasting ($p > 0.5$).

Patient groups did not significantly differ from each other on disease duration [$t(29) = 1.06$, $p = 0.30$], UPDRS III score [$t(27) = 1.44$, $p = 0.16$], H&Y score ($U = 98$, $Z = 0.30$, $p = 0.77$), LED total [$t(29) = 0.9$, $p = 0.38$], LED DA ($U = 94$, $Z = -1.03$, $p = 0.30$) and LED Levodopa [$t(29) = 1.39$, $p = 0.17$].

The PD+BE group scored significantly higher, compared to the PD group, on the QUIP-RS sub-scale for eating, buying, hobbyism and total QUIP-RS score (all $ps < 0.01$). Instead, they did not differ for gambling, hyper-sexuality, punding and compulsive medication use sub-scales (see Appendix A Table S2.2).

Questionnaires and Neuropsychological data

PD+BE scored significantly higher on HADS sub-scale of depression compared to PD (U = 60.5, Z = 2.16, p = 0.03) and C (U = 90.5, Z = 1.98, p = 0.05), which did not differ from each other (U = 150, Z = 0, p = 1). Moreover, PD+BE scored lower, compared to C on the BAS fun-seeking sub-scale while no differences were found between the PD+BE and PD, and between PD and C. PD+BE scored lower compared to C on the FAB and Semantic Fluency test, while they scored lower compared to PD on Digit Span Test. No other significant results emerged (for more details on statistics see Appendix A). See Table 2.1 and Table S2.2 (Appendix A).

	PD+BE (n=16)	**PD (n=15)**	**C (n=20)**
Gender (female)	8	7	10
Age(y)	67.1(8.2)	64.9 (12.9)	68 (6.4)
Education (y)	9.6 (4.2)	10.7 (2.9)	9.7 (3.4)
BMI	29.4 (5.9) *≠	25 (3.8)	25.2 (3.4)
PD duration (y)	8.5 (5.6)	6.8 (3.1)	--
UPDRS III	20.5 (9.6)	15.8 (8.1)	--
H&Y	1.7 (0.4)	1.7 (0.4)	--
LED total (mg)	788 (260.7)	695.7 (309.3)	--
LED-DA (mg)	181.5 (51.7)	220.6 (83.9)	--
LED-Levodopa (mg)	476.5 (231.2)	348.3 (280)	--
Total QUIP-RS score	31.6 (15.4) *	10.2 (10.2)	--
eating	8.9 (2.2) *	2 (1.8)	--
gambling	1.31 (2)	0.4 (0.9)	--
buying	4.7 (2.5) *	1.6 (1.4)	--
sex	2.7 (2.7)	1.8 (1.8)	--
hobbyism	5.8 (4.9) *	1.6 (2)	--
punding	3.5 (3.5)	1.3 (1.7)	--
DDS	3.8 (5.1)	1.4 (2.5)	--
HADS *anxiety* [a]	8.6 (4)	6.4 (3.8)	6.3 (3.5)
HADS *depression* [a]	7.6 (4.3) *≠	4.8 (2.3)	4.8 (3.2)
BIS impulsivity	60.1 (9.5)	57.4 (10.2)	63.1 (8.3)
attentional	15.6 (3.3)	14.5 (2.7)	16.3 (3.3)
motor	20.3 (3.5)	18.8 (4.5)	20.5 (3.5)
non-planning	25.1 (4.7)	28.8 (7.4)	26.3 (4.7)
BAS	38.5 (3.8)	39.2 (7.1)	40.2 (5.6)
reward responsiveness	17.5 (2.8)	16.6 (3.1)	17.6 (2.3)
drive	11.8 (1.8)	12.5 (3.9)	11.9 (2.3)
fun-seeking	9.1 (2.6)	10 (4.5)	10.6 (1.9)

Table 2.1. Demographic, neuropsychological and questionnaire data (mean and standard deviation). Sub-scales of the questionnaires are provided in Italics.
* = significantly different from PD, $p < 0.05$; ≠ = significantly different from C, $p < 0.05$; y = years; mg = milligrams; *a* = one patient didn't complete the HADS.

Self-ratings of "liking" and "wanting" for foods

The ANOVA on "liking" ratings did not show significant results (*ps* > 0.40) **(Fig. 2.1a)**. The same ANOVA on wanting ratings showed a main effect of type of food ($F_{1, 48}$ = 14.60, p < 0.001), with sweet foods wanted more (mean ± SD: 31.56 ± 17.80) relative to salty foods (mean ± SD: 23.64 ± 17.40) **(Fig. 2.1b)**. No significant differences between groups emerged (*ps* > 0.40).

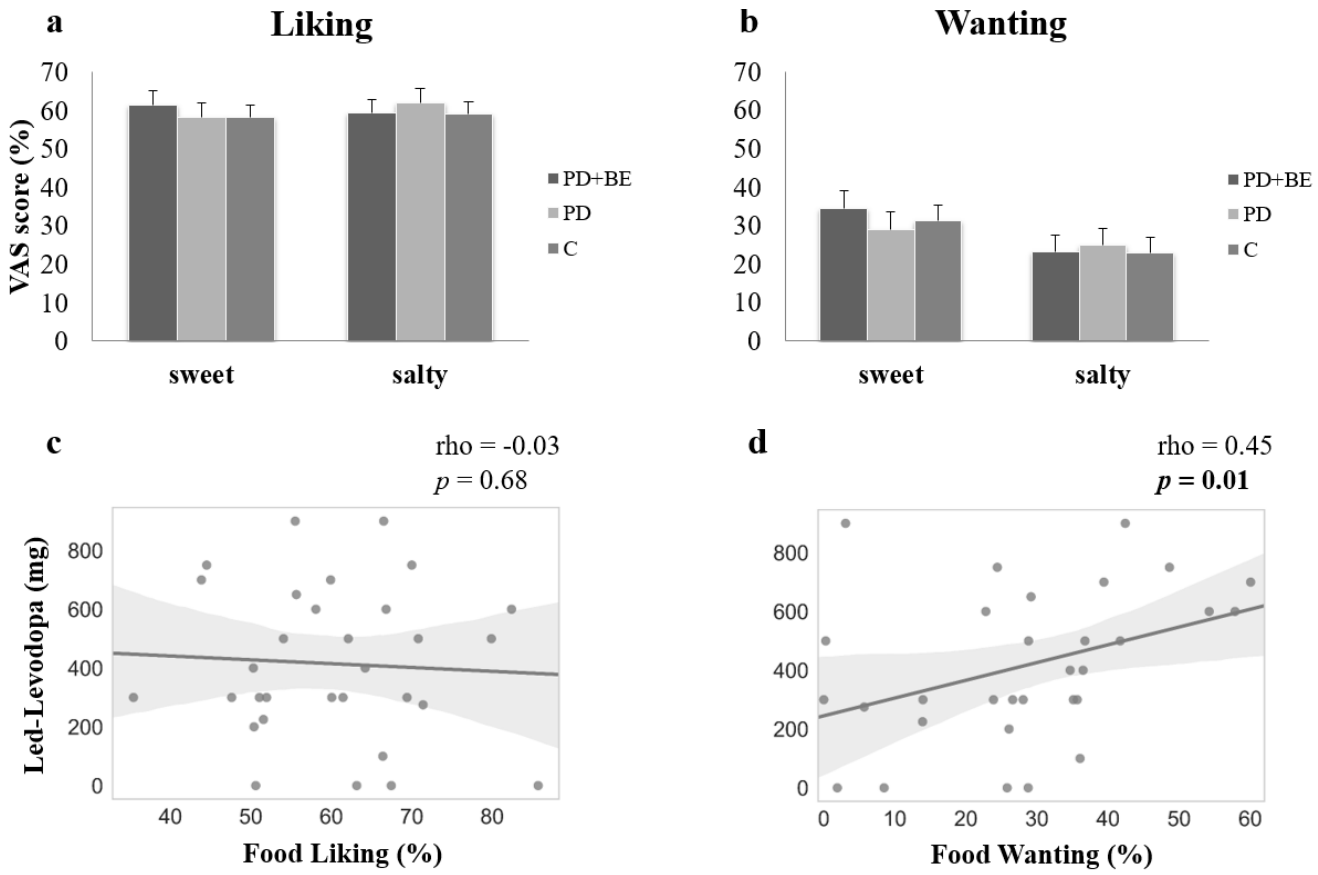

Fig.2.1. (a) Mean self-ratings of Liking and (b) Wanting for sweet and salty foods for PD+BE, PD and C participants. c) Correlations between LED-Levodopa and food Liking and (d) Wanting across all PD participants. The error bar represents standard error.

Affective Priming Task

Participants did not differ on affective priming scores associated with salty foods (PD+BE vs PD: *U* = 94, Z = -0.16, *p* = 0.87; PD+BE vs C: *U* = 130, Z = 0, *p* = 1; PD vs C: *U* = 141, Z = 0.30, *p* = 0.76).

However, PD+BE showed lower affective priming scores for sweet foods compared to C (U = 59, Z = -2.62, p < 0.01), while no differences were found between PD+BE and PD (U = 75, Z = -1.04, p = 0.30) and between PD and C (U = 98, Z = -1.73, p = 0.08) **(Fig. 2.2a)**. Importantly, participants did not differ on affective priming scores in the control condition, when food-unrelated filler pictures were presented (PD+BE vs PD: U = 66, Z = -1.45, p = 0.15; PD+BE vs C: U = 93, Z = -1.36, p = 0.17; PD vs C: U = 128, Z = 0.73, p = 0.46).

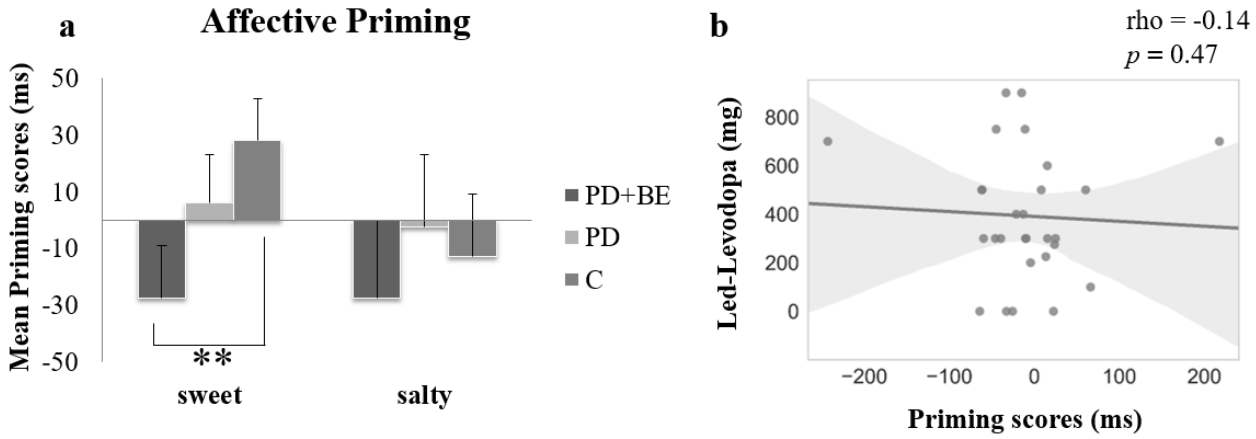

Fig. 2.2 (a) Mean affective priming scores for sweet and salty foods for PD+BE, PD and C participants. (b) Correlation between LED-Levodopa and affective priming scores for food overall across all PD participants. The error bar represents standard error.

Grip-force task

The ANOVA group (PD+BE, PD, C) x reward (sweet foods, salty foods, money) showed a significant main effect of reward ($F_{2, 96}$ = 17.04, p < 0.0001). Post hoc analysis showed that the participants' hand-grip force for sweet and salty foods was higher relative to money items (Ps > 0.0001) **(Fig. 2.3a)**. No other significant results emerged (Ps > 0.29).

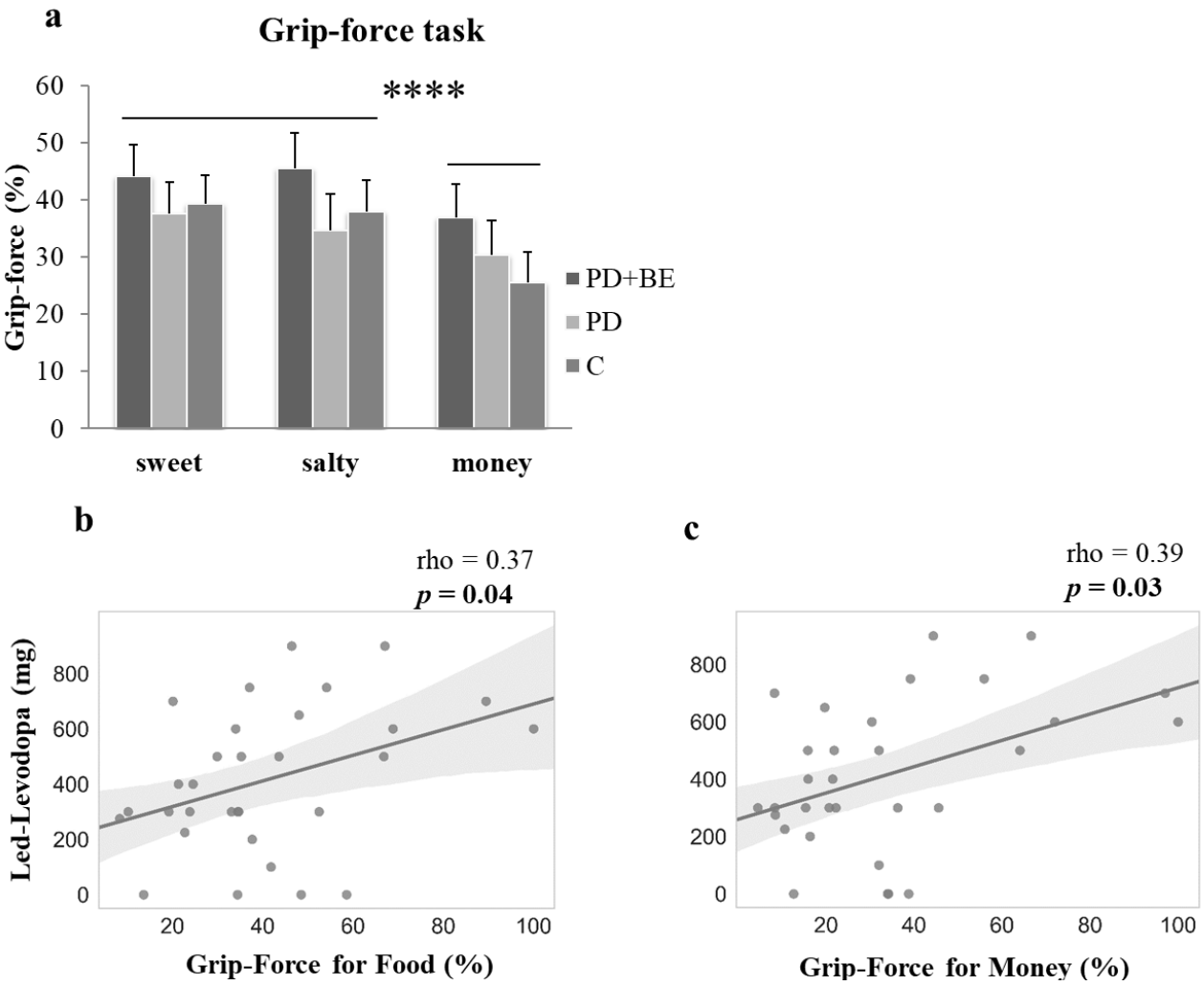

Fig. 2.3. a) Mean grip-force scores for sweet/salty foods and money for PD+BE, PD and C participants. (b) Correlation between LED-Levodopa and grip-force scores for food overall across all PD participants. (c) Correlation between LED-Levodopa and grip-force scores for money across all PD participants. The error bar represents standard error. The error bar represents standard error.

Correlational Analysis

Binge eating

Across all PD patients the QUIP-RS sub-scale for *binge eating* negatively correlated with Digit Span scores (rho = -0.43, p = 0.01) and positively correlated with the HADS sub-scale for depression (rho = 0.47, $p < 0.01$). No significant correlations were found between binge eating scores and LED-levodopa, LED-DA or LED total or other measures (see supplementary material).

LED

We found a positive correlation between LED-Levodopa and self-ratings of "wanting" (rho = 0.45, $p = 0.01$) **(Fig. 2.1d)** but not "liking" (rho = -0.03, $p = 0.86$) for food overall **(Fig. 2.1c)**. In the same way, LED-Levodopa positively correlated with the hand-grip force for both food (rho = 0.37, $p = 0.04$) (**Fig. 2.3b**) and money (rho = 0.39, $p = 0.03$) (**Fig. 2.3b**), but not with affective priming scores for foods (**Fig. 2.2b**) and non-food items (*Ps* > 0.47).

Conversely, LED-DA negatively correlated with the hand-grip force for food and money (respectively, rho = -0.49, $p < 0.01$; and rho = -0.57, $p < 0.001$).

2.4 Discussion

This study explored whether BE in PD patients is associated with increased incentive salience for food rewards. We found that patients with BE displayed an altered liking for sweet foods but not increased wanting. Importantly, this difference emerged only when implicit measures were used, while no differences emerged in self-report ratings of liking and wanting. Liking was measured with an affective priming task that assesses participants' attitudes and affective reactions in a relatively automatic way, without the need for conscious reflection (De Houwer et al., 2009). In this task, patients with BE showed a negative attitude toward sweet foods compared to controls. This result seems in line with studies reporting a less positive attitude for palatable foods in individuals with eating alterations, such as, for instance, restraint eaters (Papies et al., 2009). As it happens in unsuccessful dieters, sweet foods pose a particular challenge on PD patients with BE. Indeed, as reported by Voon et al. (2011), patients with ICDs frequently report preoccupations, the inability to control the urges or impulses, and other pathological behaviors (such as lying or stealing) that arise to act on these urges. This result is also consistent with studies reporting a preference for sweet foods in patients with PD (Aiello et al., 2015). However, this result must be interpreted with caution since no difference was observed between PD patients with and without BE. The method we used to identify binge eaters may explain this null result. As mentioned in the limitation section, the QUIP

has indeed two main limitations: first, it lacks validation in the Italian population, and second, it is a self-report measure. For these reasons, it may not be able to identify more subtle disorders. Of course, these are speculations and future studies are warranted in order to investigate these aspects.

In our study, patients with BE did not report increased wanting for food. This is at variance with several studies reporting increased ventral striatal dopamine responses in ICDs to rewards-related cues, consistently with a global sensitization to appetitive behaviors (O'Sullivan et al., 2011; Evans et al., 2006; Steeves et al., 2009; Politis et al., 2013). Two main considerations can be advanced. First, it is possible that our tasks fail to capture eventual alterations in food incentive salience. This is in line with the concerns already present in the literature about the possibility to disentangle liking and wanting in humans with behavioral tasks (Pool et al., 2016). Crucially, in our study we found that LED-Levodopa significantly correlated with the performance in tasks assessing wanting (both in the self-report measure and in the handgrip force task) and not with liking tasks. These results, that are consistent with the Incentive sensitization theory (Berridge et al., 2009), suggest that the tasks we used are able to capture the wanting component.

Second, it is possible that BE in PD patients is preferably associated with altered liking for rewards or, more in general, with affective abnormalities. Interestingly, we found an association between binge eating and depression, in accordance with previous studies on ICDs (Vriend et al., 2014). More in general, our results are, at least in part, more in line with other theories of addiction, as for instance the reward deficiency syndrome (RDS) theory (Blum et al., 2000). According to this theory, individuals with addictive behaviors exhibit a chronic hypoactivation of brain reward pathways and a reduced pleasurable experience from rewards. Importantly, addictive behaviors are believed to emerge in order to compensate for this deficiency and stimulate brain reward areas. This hypothesis has recently been extended also to the food domain (Volkow et al., 2017). More studies are thus necessary in order to clarify this issue, since this is the first study in which reward sensitivity has been investigated in patients with BE.

Interestingly, binge eaters PD patients presented lower working memory (WM) scores compared to non-binge eaters patients. Indeed, deficits in executive functions, including working memory, have been proposed as potential responsible of the phenomenology of ICDs and have been frequently reported (Weintraub et al., 2010). Moreover, WM is also one of the executive functions that have been associated with eating behaviors. More in details, WM is believed to allow individuals to maintain long-term outcome (such for instance, a healthy diet) and avoid to pursue non in line short-term goals (Dohle et al., 2017). An enhanced general susceptibility to cognitive interference of WM in the context of salient food cues has been reported for instance in studies on BE in the general population (Voon et al., 2015).

Lastly, some limitations of the study should be addressed. First, we used the QUIP-RS questionnaire instead of a clinical psychiatric assessment to distinguish PD patients with and without ICDs. Moreover, this questionnaire still lacks a validation on the Italian population. Second, differently from what observed with LED-Levodopa, a negative correlation between LED-DA and the grip force task assessing wanting was obtained. Although both levodopa and dopamine agonists stimulate dopamine receptors, they have different pharmacokinetic characteristics, which may explain this result; moreover, dopamine agonists also differ between each other (Poletti et al., 2013).

In conclusion, our results showed that binge eating in PD is associated with cognitive abnormalities, and to lesser extent affective abnormalities, but not with increased incentive salience. More studies are necessary in order to further understand the mechanisms underlying BE in PD. This aim is particularly important considering that this disorder not only affects patients' lives, but also it exposes them to negative health outcomes.

Study 2

The role of the prefrontal cortex in Parkinson's patients with impulse control disorders: neuromodulation of reward sensitivity and temporal discounting of rewards

Abstract

In this study we aimed to test whether higher reward responsiveness (liking and wanting) and greater temporal discounting of rewards were present in PD+ICD patients. Moreover, we explored whether anodal tDCS over the left DLPFC could be effective in restoring such possible alterations.

We studied 15 PD patients with ICD, 13 PD patients without ICD and 15 healthy matched controls. These participants performed a reward responsiveness task employing both explicit (self-ratings of liking and wanting) and implicit (heart beat and skin conductance response) measures, as well as two temporal discounting tasks with food and money rewards in order to assess their reward valuation processes. Each participant performed the experimental tasks during active anodal tDCS of the left dorsolateral prefrontal cortex (DLPFC), anodal tDCS of the primary motor cortex (M1) and sham tDCS.

Results showed a greater reward responsiveness (for both liking and wanting) and a steeper temporal discounting of rewards in PD+ICD patients compared to controls. Moreover, we found that tDCS may be capable to modulate the altered intensity of PD+ICD patients' liking, but not their altered wanting and temporal discounting of rewards. These findings suggest that anodal tDCS over the left DLPFC may modulate only the affective component of their altered reward responsiveness, and help to further understand the neural mechanisms underlying ICD in PD.

2.5 Introduction

As already discussed in the Introduction (see paragraph 1.3) and in Study 1, patients with PD may develop ICD such as gambling, binge eating, compulsive shopping and others (Voon et al.,

2017). Although several studies have reported the negative impact of these disorders on patients' lives, there are no evidence based recommendation for their treatment, except the reduction of dopaminergic medication that, however, may be an unsatisfactory option for the patient because it can worsen motor control (Weintraub et al., 2010; Voon et al., 2017). The role of abnormal mesocorticolimbic dopaminergic system function has been constantly reported in ICD, and both reward responsiveness and reward valuation alterations have been proposed as potential responsible of the phenomenology of these disorders in PD (see Chapter 1.3). Particularly, it has been reported that PD patients with ICD showed enhanced reward responsiveness to reward cues in neuroimaging studies (Evans et al., 2006; O'Sullivan et al., 2011; Politis et al., 2013; Loane et al. 2015) and greater delay discounting in behavioral studies employing intertemporal choice tasks (Voon et al., 2010; Housden et al., 2010). In addition, cognitive deficits such as working memory impairment, dysfunction of abstraction ability and set-shifting abilities, which may affect reward responsiveness and reward valuation processes, have been documented in PD-ICDs patients (Santangelo et al., 2017). In line with these evidences, both PET and fMRI studies have linked the presence of ICDs to alterations not only of striatal but also frontal brain regions such as the prefrontal cortex (PFC), the orbitofrontal cortex (OFC) and the cingulate cortex (O'Sullivan et al., 2011; Steeves et al., 2009; Cilia et al., 2011; vanEimeren et al., 2010; Voon et al., 2010; Politis et al., 2013). Patterns of atrophy in these regions have also been reported in morphometric studies (Pellicano et al., 2015; Biundo et al., 2015), suggesting their role in the inability of PD patients with ICD to resist an impropriate drive. Despite these evidences, the neural mechanisms underlying aberrant reward responsiveness and reward valuation in PD patients with ICD remain unclear (Voon et al., 2017, Girard et al., 2019).

Transcranial direct current stimulation (tDCS) is a technique increasingly used in the last years (Lefaucher et al., 2017; Lapenta et al., 2018). tDCS is a safe and painless procedure able to modulate brain activity (Fertonani and Miniussi, 2017). A low-amplitude direct electrical current (typically 1–2 mA) is applied though electrodes by a constant-current device to the human skull resulting in increased cortical activity under the anode and decreased activity under the cathode (Woods et al.,

2016). In particular, it has been shown that the application of tDCS to the dorsolateral prefrontal cortex (DLPFC) can reduce craving for rewards (Boggio et al., 2008; Fregni et al., 2008) and improve reward valuation processes and risk-taking (Fecteau et al.,2007, 2014; Knoch et al., 2008; Boggio et al.,2010). Interestingly, it has been proposed that anodal tDCS over the DLPFC may enhance executive function and improve cognitive control, and thus reduce the probability of relapse to drug use (da Silva et al., 2013). Thus, the neuromodulation of the DLPFC may have potential therapeutic application to remodel altered brain circuits that are involved in reward responsiveness, reward valuation and more in general in cognitive control (Spagnolo and Goldman, 2017).

Despite the potential utility of this technique for ICD in PD, so far, none of the published studies has specifically evaluated the efficacy of tDCS over the dorsolateral prefrontal cortex on PD patients with these disorders. However, several studies have already documented the beneficial effects of tDCS on behavioral and cognitive symptoms in PD (for a recent review see Dinkelbach et al., 2017). For instance, Boggio et al. (2006) studied 18 patients with idiopathic PD, which performed a working memory task during active anodal tDCS of the left DLPFC, anodal tDCS of the primary motor cortex (M1) or sham tDCS. They observed a significant improvement in working memory in terms of task accuracy after anodal tDCS of the left DLPFC compared to the other two conditions. In another study on PD patients, anodal tDCS over the DLPFC showed a beneficial effect on executive functions measured through the Trial Making Test (Doruk et al., 2014). Recently, Benussi et al. (2017) found that the cathodal tDCS over the right DLPFC increased scores in the Iowa Gambling Task, a test assessing reward valuation abilities. According to the authors, the inhibitory stimulation of the right DLPFC could produce a facilitation of the left DLPFC due to interhemispheric competition (Benussi et al., 2017).

A possible mechanism explaining such beneficial effects is the modulation of fronto-striatal dopamine function (Fukai et al., 2019; Fonteneau et al., 2018). More in details, tDCS and repetitive transcranial magnetic stimulation (rTMS) to the left DLPFC can modulate executive functions by

inducing dopamine release in the anterior cingulate cortex, orbitofrontal cortex and striatum (Fonteneau et al., 2018; Fukai et al., 2019; Cho and Strafella, 2009).

Since frontal and striatal dopamine dysfunction in PD are related to decline in executive function (Sawamoto et al., 2008; Christopher et al., 2014), dopaminergic stimulation of DLPFC through tDCS might be particularly critical in PD patients with ICDs, which usually show higher frontal and striatal dysfunctions compared to those without ICDs (Voon et al., 2017; Santangelo et al., 2017). Therefore, by targeting DLPFC, anodal tDCS may enhance cognitive control over altered reward responsiveness and reward valuation processes by restoring frontal-striatal circuitry abnormalities of PD patients with ICDs. Using both a sham and an active control condition (stimulation of the primary motor cortex (M1)), in this study we tested this hypothesis by comparing PD patients with and without ICDs and healthy matched control in tasks assessing reward responsiveness and reward valuation processes. We measured participants' reward responsiveness through explicit measures such as self-rating of liking and wanting of different rewards and non-rewards stimuli (Terenzi et al., 2018). Moreover, during the task we recorded psycchophysiological measures such as heart rate and skin conductance responses, which have been related to the hedonic valence (or implicit liking) and the arousal (or implicit wanting) of a stimulus, respectively (Kuoppa et al., 2016; Cecchetto et al., 2017; Foroni et al., 2016). In addition, in order to explore reward valuation processes, we used two temporal discounting tasks with both food and money rewards (Sellitto et al., 2010).

In summary, the present study aims at testing the hypothesis that PD patients with ICDs (PD+ICD) may show higher reward responsiveness and steeper temporal discounting of rewards compared to PD patients without ICD (PD) and healthy matched controls (C). Moreover, it aims at testing whether anodal tDCS over left-DLPFC may have a beneficial effect on altered reward responsiveness and reward valuation processes of PD+ICD patients.

2.6 Material and Methods

Subjects

Twenty-eight dopaminergic treated patients with PD and fifteen healthy controls took part in the study. PD patients were recruited from the movement disorders clinic of "Cattinara" hospital in Trieste (Italy). Exclusion criteria were: (a) co-morbidity for other neurological illnesses other than PD; (b) physical inability to attend the experiment such as incapacitating dyskinesia; (c) not meeting eligibility criteria for tDCS such as having a history of seizures or implanted metal objects or heart problems (see Fertonani et al., 2010). Patients were assessed by a neurologist for the presence of ICD and were also asked to fill the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) (Weintraub et al., 2012). On the basis of the clinical evaluation made by the neurologist as well as on QUIP-RS proposed criteria for single and combined ICD (Weintraub et al., 2012), fifteen PD participants were identified as having impulse control disorders (PD+ICD). The other thirteen PD patients (PD) and fifteen healthy controls (C) had no history of ICD. As in Study 1, patients' disease severity was assessed using the Unified Parkinson's Disease Rating Scale-Part III (UPDRS-III) and the Hoehn and Yahr scale (H&Y) (Hoehn and Yarhr, 1967). In addition, for each patient a daily L-dopa equivalent dose (LED total) was calculated based on Tomlinson et al. (2010). All participants gave written informed consent to participate in the study that was approved by SISSA Ethics Committee. For details on demographical and clinical data, see Table 2.2.

Experimental procedure

We used a crossover and counterbalanced design (see Figure 2.4). Subjects underwent the identical protocol design in three sessions for each experimental condition (anodal DLPFC, M1 and Sham tDCS) in which they were asked to perform a reward sensitivity task and two temporal discounting tasks. Each participant attended all sessions, which were 7 days apart to avoid cumulative increases

in cortical excitability (Alonzo et al., 2012; Ammann et al., 2017). At the beginning of the first session, as in Study 1, participants' weight and height were collected and body mass index (BMI) was then calculated. Moreover, in each session we collected participant's subjective ratings of hunger and fasting in order to control for macroscopic differences between subjects. In the first session, participants were also asked to undergo some neuropsychological tasks and complete several questionnaires.

Direct current stimulation protocol

During the experiment, tDCS was administered with a battery driven DC stimulator (Eldith, NeuroConn) connected with a pair of electrodes: an anode electrode with an area of 25 cm^2 and a cathode electrode with an area of 70 cm^2. Electrodes conductance was ensured through the use of a saline solution and conductive gel. To stimulate the LDLPFC (DLPFC session), the anode electrode was positioned over F3 location (in 10–20 nomenclature for EEG electrode positioning), whereas the cathode electrode was placed extra-cephalically on the right upper arm (Mengotti et al., 2018; Osimo et al., 2019; Doruk et al., 2014) (see Fig 2.4). We used this extra-cephalic montage in order to isolate the effect of the current flow direction, as much as possible, to the LDFPFC (Kabakov et al., 2012; Noetscher et al., 2014). Although we used a relatively accurate method to localize LDPFC (Herwig et al., 2003), in order to test whether possible effects of LDPFC were specific, we stimulate the primary motor cortex (M1) in another session (M1 session) (Boggio et al., 2006). Particularly, in this session the anode electrode was placed over C3 EEG-location (DaSilva et al., 2011; Boggio et al., 2006), whereas the cathode electrode was kept on the right upper arm. Finally, a sham stimulation (Sham session) was also performed. In this stimulation, the electrodes were placed in same positions as in the DLPFC session (Boggio et al., 2006).

In the DLPFC and M1 sessions, the current intensity of 1.5 mA (current density of 0.06 mA/cm2) was delivered for 20 minutes, including two ramping periods of 15 s at the beginning and at the end of the stimulation. The stimulation started 60 s before the beginning of the experimental

tasks. In the sham session, the current was supplied only during the first 30 s (15 fade-in phase and 15 fade-out phase) in order to ensure that the participants felt the tingling/itching sensation. A questionnaire about sensations experienced during the stimulation was completed by participants at the end of each session (Fertonani et al., 2015). No differences between the sensations experienced during the three sessions emerged, as shown by Friedman ANOVAs (all *ps* > 0.28). Lastly, in order to control for possible effects of tDCS on mood (Austin et al., 2016), we administered the Profile of Mood states (POMS) (Grove and Prapavessis, 1992) immediately before (as a baseline) and after every stimulation. No differences in mood emerged between the three sessions, as shown by a Friedman ANOVA [χ^2 (2) = 2.17, p = 0.34].

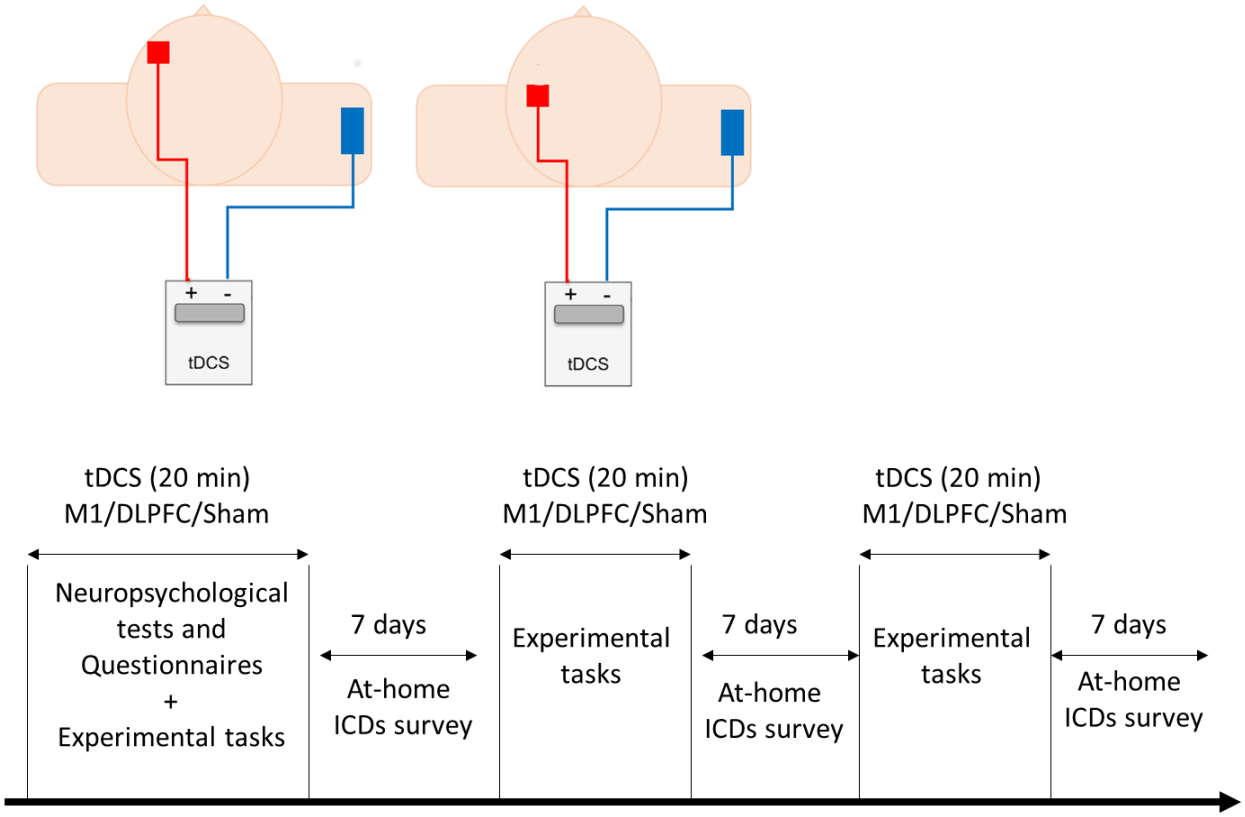

Figure 2.4. Electrode placement for anodal tDCS of DLPFC (left) and M1 (right). The sham stimulation had the same setup as the anodal tDCS of DLPFC, but after the ramping up period of 15 s the current between the electrodes stopped (top). The experimental protocol design. Each subject was tested during sham, active M1 and LDLPFC stimulation (bottom).

Reward sensitivity task

While viewing 24 images, participants used a computerized visual analogue scale (VAS) ranging from 1 (very little) to 7 (very strong) to rate how much they ‘‘liked the picture’’ (liking rating), and how much they ‘‘would have it now’’ (wanting rating). Pictures included equal proportions of appetizing foods, gambling, shopping and familiar dopamine replacement therapies, as well as appealing but not appetizing neutral images (e.g., a laptop, a glass of water) according to a procedure already used in O'Sullivan et al. (2011). These reward and non-reward images were previously selected through a questionnaire filled out by an independent sample of participants (n = 53) and were matched for several variables such as brightness, visual complexity, arousal, valence and familiarity (see Appendix A for detailed statistics).

Figure 2.5 illustrates the experimental paradigm. Each trial began with a 2 s fixation screen, followed by the presentation of the image for 4 s and a blank screen for 8 s. After that, participants provided their self-ratings of liking and wanting.

Psychophysiological data acquisition and analysis

SCR and HR were recorded during the reward sensitivity task with the data acquisition unit MP150 (BIOPAC Systems, Inc.) with a sampling rate of 1000 Hz.

SCR was acquired through Ag/AgCl electrodes attached to the palmar index and the middle finger of the hand and processed with AcqKnowledge Version 4.1 (BIOPAC Systems, Inc.) by resampling data to 125 Hz and applying a low-pass filter (Blackman−92 dB, 1 Hz) (Petschow et al., 2016; Stussi et al., 2015; Braithwaite et al., 2013). SCR was then computed as the maximum amplitude in μSiemens (μS) between 1 and 4 s after event onset (picture presentation) and corrected for a baseline of 2 s before event onset (Petschow et al., 2016). Peak amplitudes were square root transformed to improve interpretability (Braithwaite et al., 2013).

Participants' HR was measured via three surface electrodes placed on the torso in a lead III configuration. Beat detection was performed using automated routines in Acqknowledge software. Frequency was computed as beats per minute (bpm) during the 4 s of stimulus presentation and then corrected by subtracting a 2 minute resting baseline (Garland et al., 2014) recorded for each participant before the reward sensitivity task to obtain the instantaneous heart rate (IHR) (Palomba et al., 2000; Cecchetto et al., 2017). HR values of one subject in sham and M1 sessions and HR values of two subjects in M1 and DLPFC (respectively) sessions were excluded from the analysis due to noisy signal.

Temporal discounting task

Participants performed two computerized temporal discounting tasks in which they made choices between an amount of reward that could be received immediately (immediate option) and an amount of reward that could be received after some specific delays (delayed option) (Sellitto et al., 2010). Specifically, after the presentation of a fixation cross (1 s), a choice between the immediate and the delayed option was presented. In each choice the amount of the reward, the image of the reward and the delay of delivery were displayed. Participants made their choices by pressing one of two buttons (see Fig. 2.5). After that, the chosen option remained on the screen for 1 s. The inter-trial interval was 1.5 s. Participants were asked to make five choices per block. Each block corresponded to a specific delay: 2 days, 2 weeks, 1 month, 3 months, 6 months and 1 year. An adjusting amount procedure was used across blocks to determine participants' discounting rates. More specifically, the first choice presented to participants was always between 20 units for the immediate option and 40 units for the delayed one. During the task, the delayed option remained fixed; on the other hand, the immediate option was adjusted using a staircase procedure (Myerson et al., 2003). Thus, when the immediate option was chosen, in the following choice the amount of this option was decreased by half of the difference between the delayed and the immediate option. Conversely, when the delayed option was chosen, in the following choice the amount of the immediate option was increased. The size of the

adjustment of the immediate option during trials was always half of the previous adjustment. After five choices for a specific delay, the participant began a new series of choices with another delay. The subjective value for each block was estimated as the immediate amount that would have been presented on the sixth trial. In one task, we used food (primary reward) while in another we used money (secondary reward). All rewards were hypothetical. For what concerns the food task, participants were asked to choose their preferred food from a selection of six popular snacks (to increase task ecological validity, snacks usually present in the vending machines were used as stimuli). One participant did not perform the temporal discounting task with money rewards in the sham session due to technical problems.

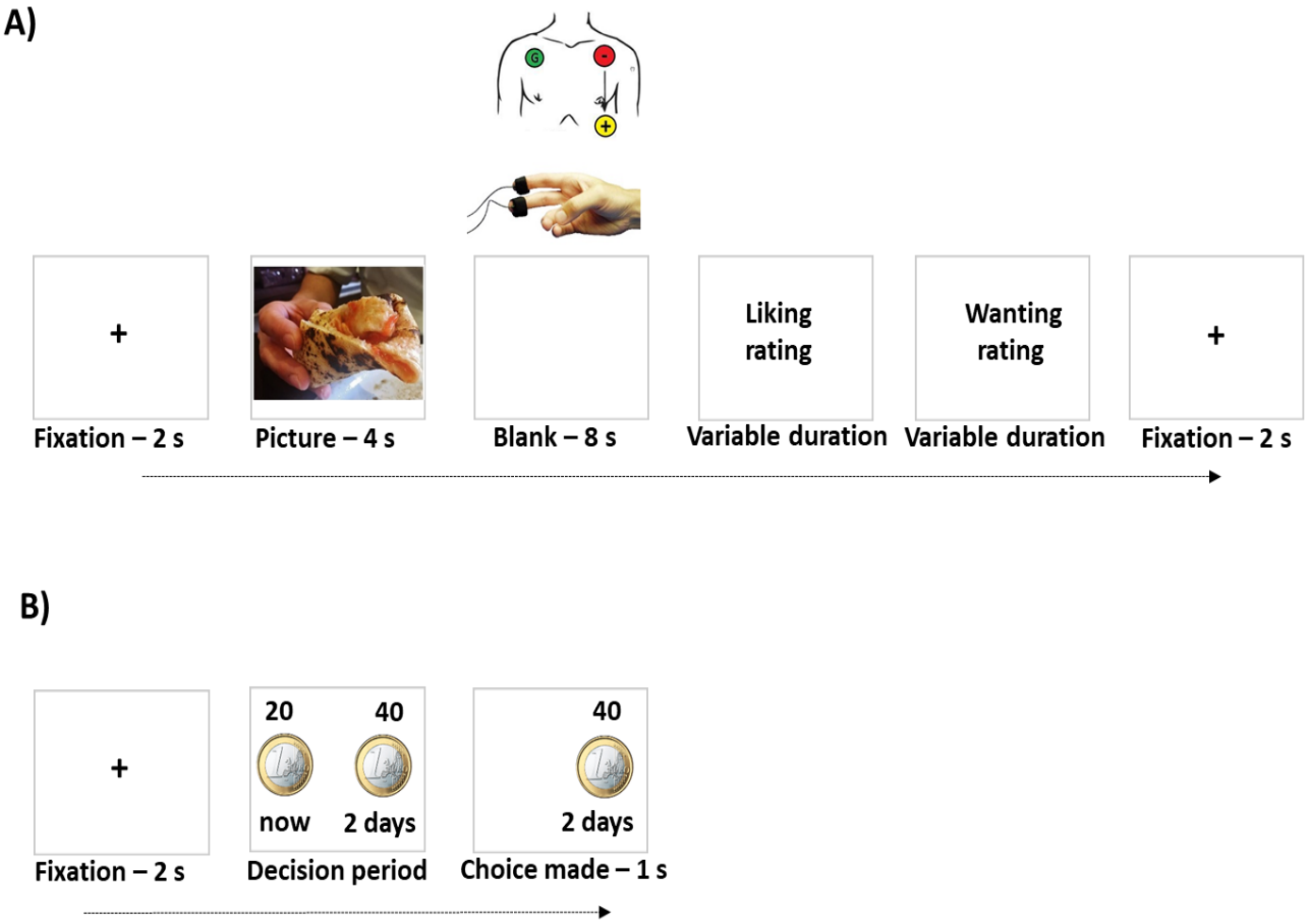

Figure 2.5. Reward sensitivity task (top). Example trial sequence. Each trial began with a 2 s fixation screen, followed by the presentation of the image for 4 s and a blank screen for 8 s. During the presentation of the image HR was recorded, while SCR was recorded between 1 and 4 s after picture onset. After that, participants provided their self-ratings of liking and wanting. Temporal discounting task (bottom). Example trial sequence with money rewards. In each trial, after 2 s

fixation period, participants chose between a small/immediate amount of reward and a large/delayed one. The chosen option remained on the screen for 1 s.

Clinical and neuropsychological evaluation

All participants completed the Mini Mental State Examination (MMSE) (Measso et al., 1993), the Digit Span Forward test (Orsini et al., 1987), the Corsi test (Spinnler and Tognoni, 1987) and filled the Hospital Anxiety and Depression Scale (HADS).

Statistical Analysis

Data were analyzed using Statistica 8.0 (StatSoft, USA) software. Parametric and non-parametric tests were used where appropriate. Kolmogorov-Smirnov test was undertaken to demonstrate that data were normally distributed. We compared groups (PD+ICD, PD, C) on demographic, neuropsychological and questionnaire measures. For the reward sensitivity task, we compared the three groups in the three different sessions (M1, DLPFC, Sham) for their self-ratings of liking and wanting and their SCR and IHR for reward and non-reward related pictures.

For the temporal discounting tasks, we assessed the temporal discounting hyperbolic parameter *k* in order to measure how subjective values of rewards decay with delays (Mazur, 1987; Green and Myerson, 2004; Sellitto et al., 2010). Moreover, we calculated the area under the empirical discounting curve (AUC) as a model-free parameter (Myerson et al., 2001). Parametric Pearson and non-parametric Spearman correlations were used to examine the relationship between demographic, clinical, physiological and behavioral measures. Importantly, since it has been shown that older subjects respond less to tDCS, age was used as covariate in the analyses of the behavioral tasks as well as in the correlation analyses (Fertonani et al., 2014; Boggio et al., 2006; Antonenko et al., 2018).

2.7 Results

Demographic, clinical, questionnaires and neuropsychological data

PD+ICD, PD and C were matched for gender, age, education and BMI. Moreover, they were not different on hunger levels and hours of fasting across the three experimental sessions (*Ps* > 0.16) (see Appendix A for detailed statistics).

One-way ANOVAs with group as factor (only patient) did not show significant differences on disease duration ($F_{1, 26} = 0.84$, $p = 0.37$), UPDRS-III score ($F_{1, 26} = 0.64$, $p = 0.43$), LED total ($F_{1, 26} = 1.28$, $p = 0.27$), LED-Dopamine agonists ($F_{1, 26} = 0$, $p = 0.98$) and LED Levodopa ($F_{1, 26} = 0.59$, $p = 0.45$). A Kruskal-Wallis ANOVA on H&Y scores showed no significant results as well [χ^2 (1) = 0.11, p = 0.74].

Compared to PD and C, PD+ICD scored significantly higher on the QUIP-RS sub-scales for *eating*, *hobbysm*, *punding*, *hyper-sexuality* (in this sub-scale the difference with PD participants was marginally significant, $p = 0.06$), as well as on the *combined ICDs* sub-scale (pooling together eating, gambling, buying and hyper-sexuality) and the *QUIP-RS total score* (all *ps* < 0.02). Furthermore, PD+ICD participants scored higher on the *compulsive medication use* sub-scale compared to PD participants ($p = 0.03$). PD participants scored significantly higher on the *eating* sub-scale compared to C participants ($p < 0.01$), while no significant differences emerged for the other sub-scales as well as for *QUIP-RS total score* (all *ps* > 0.08). The three groups of participants were not statistically different on *gambling* and *buying* sub-scales (*ps* > 0.51). See Table 2.2 and Appendix A for detailed statistics.

PD+ICD participants scored higher on the HADS anxiety sub-scale compared to C participants ($p <$ 0.01). No other significant results emerged on this questionnaire (*ps* > 0.11) (see Appendix A).

Lastly, a Kruskal-Wallis ANOVA on MMSE scores showed a main effect of group [$\chi 2$ (2) = 7.56, p = 0.02]. C participants scored higher (Mann–Whitney U test) on this test compared to PD+ICD (U = 61.00, Z = 2.22, $p = 0.03$) and PD (U = 45.00, Z = 2.53, $p = 0.01$), while no significant differences emerged between PD+ICD and PD (U = 95.05, Z = -0.09, $p = 0.92$). No significant results emerged

from Kruskall-Wallis ANOVAs on Digit Span test scores [$\chi 2$ (2) = 3.10, p = 0.21] and Corsi test scores [$\chi 2$ (2) = 1.93, p = 0.38].

	PD+ICD (n=15)	**PD (n=13)**	**C (n=15)**
Gender (female)	4	4	5
Age(y)	70.8(6.5)	72.7 (5.2)	72.2 (4.4)
Education (y)	10.9 (4.1)	12.2 (4.4)	12.4 (3.7)
BMI	26.3 (3.2)	25 (3.3)	26.2 (4.2)
PD duration (y)	8.3 (3.9)	7.1 (3.2)	--
UPDRS III	22.1 (12.6)	26.2 (15.1)	--
H&Y	1.8 (0.6)	1.8 (0.4)	--
LED total (mg)	685.3 (324.1)	568.5 (195.9)	--
LED-DA (mg)	174.7 (84.1)	173.8 (58)	--
LED-Levodopa (mg)	386.7 (195.9)	334.6 (157)	--
Total QUIP-RS score	20.9 (10.3)**##	4.8 (2.1)	2.4 (3)
Combined ICDs	10.8 (5.4)**##	3.4 (1.2)≠	1.7 (1.9)
eating	6.9 (3.6)**##	1.8 (0.9)##	0.6 (1.2)
gambling	0 (0)	0. (0)	0 (0)
buying	1.6 (2.8)	1.1 (1)	0.7 (1.1)
sex	2.3 (3.3)≠	0.5 (0.8)	0.3 (0.6)
hobbyism	5 (2.7)**##	1.1 (0.3)	0.5 (0)
punding	2.3 (3.7)**##	0 (0)	0.2 (0.5)
DDS	2.7 (3.8)*	0.3 (0.6)	--
HADS *anxiety* [a]	7.7 (2.9)	6.1 (2.5)	4.4 (2.5)
HADS *depression* [a]	5.8 (3.1)	5.5 (2.9)	3.7 (3.2)
MMSE	28.3 (1.3)≠	28.1 (1.3)≠	29.3 (0.8)
Digit Span Forward	6.3 (1.4)	5.7 (1.1)	6.5 (1.1)
Corsi test	4.9 (1.2)	4.4 (0.7)	5.1 (0.7)

Table 2.2. Demographic, clinic, questionnaire and neuropsychological data (mean and standard deviation).
Sub-scales of the questionnaires are provided in italics.
* = significantly different from PD, $p < 0.05$; ** = significantly different from PD, $p < 0.01$; ≠ = significantly different from C, $p < 0.05$; ## = significantly different from C, $p < 0.01$; y = years; mg = milligrams; DDS = dopamine dysregulation syndrome *a* = two C participants did not complete the HADS

Reward sensitivity task

A repeated-measure ANCOVA (controlling for age) on *liking ratings* with Group (PD+ICD, PD, C) as a between-subjects variable and Session (Sham, DLPFC, M1) and Stimuli (rewards, non-rewards) as within-subjects variables yielded a significant interaction Group x Session ($F_{2, 78}$ = 2.59, p = 0.04). No other significant results emerged (all *ps* > 0.07) (see Appendix A for detailed statistics). Post-hoc analysis showed that, independently of the type of the stimulus, in the Sham session

PD+ICD liked more the stimuli compared to PD (p = 0.04), while no differences emerged in this session between C and PD+ICD (p = 0.72) and between C and PD (p = 0.09). In the M1 session, PD+ICD and C liked more the stimuli compared to PD (PD+ICD vs PD: p < 0.01; C vs PD: p = 0.04) while no differences emerged between PD+ICD and C (p = 0.22). No differences between groups emerged in the DLPFC session (all ps > 0.23). See Figure 2.6.

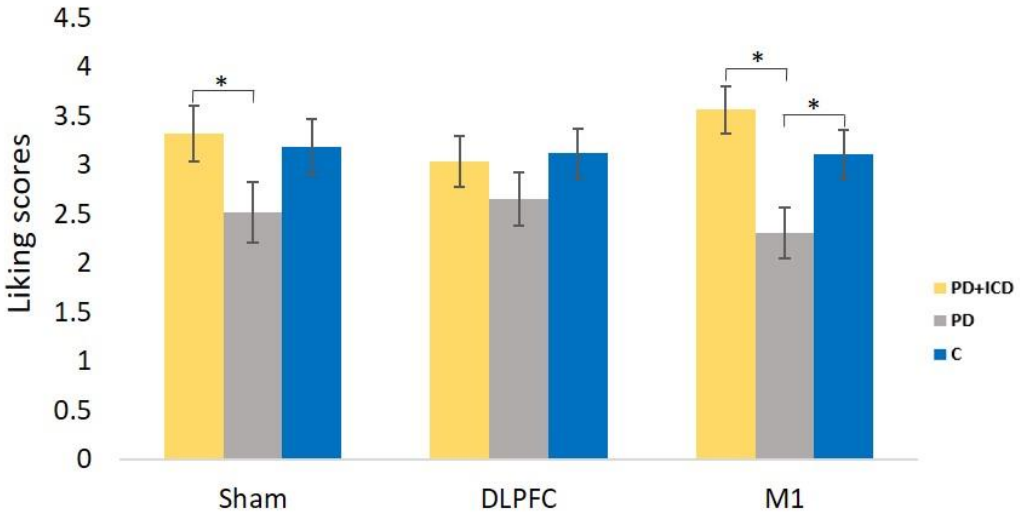

Figure 2.6. Mean self-ratings of Liking across the experimental sessions for PD+ICD, PD and C participants. The error bars represent standard error. * = p < 0.05.

A repeated-measure ANCOVA (controlling for age) on *wanting ratings* with Group (PD+ICD, PD, C) as a between-subjects variable and Session (Sham, DLPFC, M1) and Stimuli (rewards, non-rewards) as within-subjects variables yielded a significant main effect of Group ($F_{2, 39}$ = 3.99, p = 0.03) and a marginally significant interaction Group x Stimuli ($F_{2, 39}$ = 3.09, p = 0.057). No other significant results emerged (all ps > 0.12) (see Appendix A for detailed statistics). Post-hoc analysis on the main effect of group showed a higher wanting for PD+ICD participants compared to PD participants (p = 0.01) and C participants (p = 0.04), while no differences emerged between PD and C participants (p = 0.54). As regards the marginally significant interaction Group x Stimuli, independently of the session, PD+ICD wanted more rewards compared to PD (p = 0.046) and C (p = 0.01), while no differences emerged between PD and C (p = 0.63). Moreover, PD+ICD wanted also more non-reward compared to PD (p < 0.01), while no differences emerged between PD+ICD and C

(p = 0.23) and between PD and C (p = 0.11). No differences emerged between sessions ($F_{2, 78}$ = 1.34, p = 0.44). See Figure 2.7.

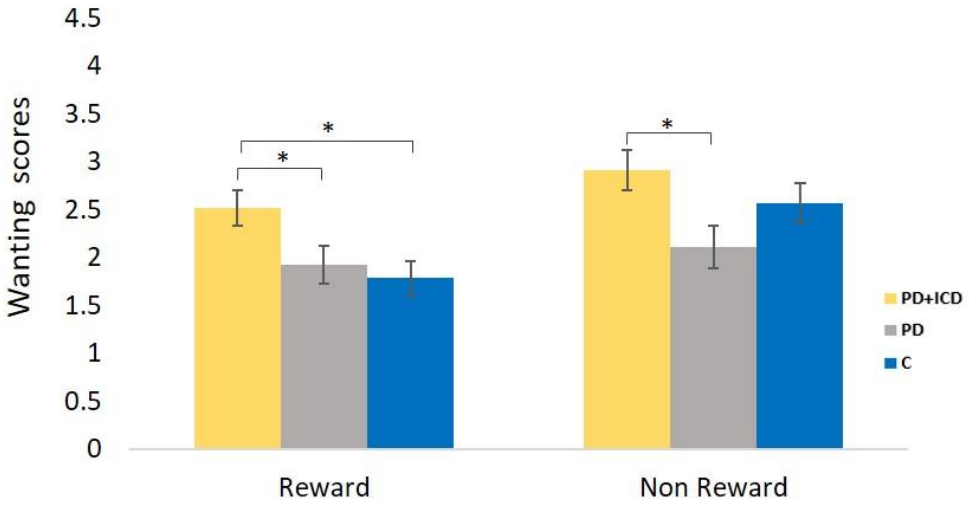

Figure 2.7. Mean self-ratings of Wanting for reward and non-reward pictures for PD+ICD, C and PD participants. The error bars represent standard error. * = $p < 0.05$.

A repeated-measure ANCOVA (controlling for age) on *HR values* during the presentation of the stimuli with Group (PD+ICD, PD, C) as a between-subjects variable and Session (Sham, DLPFC, M1) and Stimuli (rewards, non-rewards) as within-subjects variables yielded no significant results (all *ps* > 0.16). The same ANCOVA on *SCR magnitude values* during the presentation of the stimuli yielded no significant results (all *ps* > 0.08). See Appendix A for detailed statistics.

Temporal discounting task

A repeated-measure ANCOVA (controlling for age) on AUC values with Session (Sham, DLPFC, M1) and type of Task (money, food) as within-subjects variables and Group (PD+ICD, PD, C) as a between-subjects variable yielded no significant results (all *ps* > 0.10) (see Appendix A for detailed statistics).

A repeated measure ANCOVA (controlling for age) on hyperbolic log-transformed *K* values with Session (Sham, DLPFC, M1) and type of Task (money, food) as within-subjects variables and

Group (PD+ICD, PD, C) as a between-subjects variable values showed a main effect of Group ($F_{2, 38}$ = 4.02, p = 0.02). Post hoc analysis showed that, independently of the type of task, the discounting rate of PD+ICD was steeper compared to that of PD (p = 0.02) and C (p = 0.02) participants, while discounting rates of PD and C participants were not different (p = 0.84). No other significant results emerged (all *ps* > 0.12). See Figure 2.8.

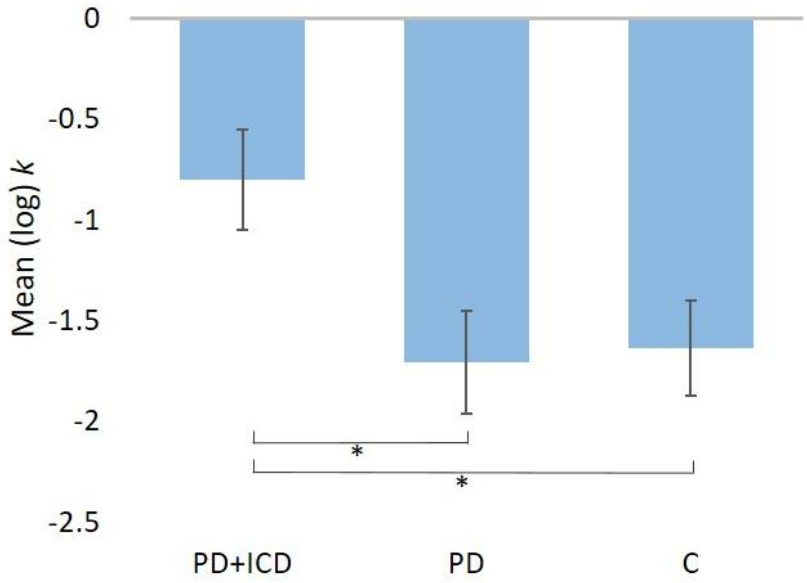

Figure 2.8. Mean (log) *K* hyperbolic values for rewards for PD+ICD, C and PD participants. The error bars represent standard error. * = p < 0.05.

Correlational Analyses

As regards the reward sensitivity task (see Table 2.3), QUIP combined ICD subscale scores positively correlated with liking scores for rewards in the Sham session (r = 0.51, p < 0.01) and in the M1 (r = 0.46, p = 0.02) session, as well as with liking scores for non-rewards in these two sessions (Sham: r = 0.43, p = 0.02; M1: r = 0.54, p = 0.02), while no correlations between liking scores for both rewards and non-rewards emerged during the DLPFC session (all *ps* > 0.06). QUIP combined ICDs scores positively correlated with wanting scores for rewards in the Sham (r = 0.58, p < 0.01), DLPFC (r = 0.41, p = 0.03) and M1 (r = 0.58, p = p < 0.01) sessions, as well as with wanting scores for non-

rewards in the Sham (r = 0.43, p = 0.03) and in the M1 (r = 0.54, p < 0.01) sessions, while no significant correlation emerged with these stimuli during the DLPFC session (r = 0.27, p = 0.18).

As regards the temporal discounting task (see Table 2.3), QUIP combined ICDs score negatively correlated with AUC values for food in the DLPFC session (r = -0.40; p = 0.04) and in the M1 session (r = -0.43; p = 0.03), but not in the Sham session (r = -0.22; p = 0.26). Moreover, QUIP combined ICDs scores positively correlated with (log) *K* hyperbolic values for food during the M1 session (r = 0.44; p = 0.02). No other significant results emerged (all *ps* > 0.07). Similar correlations emerged between QUIP-total scores and experimental tasks (see Appendix A, Table S2.5).

No significant correlations emerged between QUIP combined ICD scores with both HR values and SCR magnitude values (all *ps* > 0.06).

	QUIP combined ICDs		
	Sham	*DLPFC*	*M1*
Reward sensitivity task			
Liking rewards	**0.51****	0.37	**0.46***
Liking non-rewards	**0.43***	0.27	**0.45***
Wanting rewards	**0.58****	**0.41***	**0.58****
Wanting non-rewards	**0.43***	0.27	**0.54****
HR values rewards	0.22	-0.05	-0.10
HR values non-rewards	0.18	-023	-0.03
SCR magnitude rewards	-0.04	0.12	0.14
SCR magnitude non-rewards	-0.14	0.20	-0.11
TD task			
AUC food	-0.22	**-0.40***	**-0.43***
AUC money	-0.19	-0.17	-0.19
K hyperbolic food	0.16	0.33	**0.44***
K hyperbolic money	0.23	0.21	0.14

Table 2.3. Correlations between QUIP combined ICD subscale scores and experimental tasks measures (across all PD patients) across stimuli and experimental sessions. * = p < 0.05; ** = p < 0.01

LED

We found positive correlations between LED-Levodopa and self-ratings of wanting for non-rewards in the Sham session (r = 0.41, p = 0.03) and in the DLPFC session (r = 0.40, p = 0.04). No other significant results emerged (all ps > 0.06). As regards the physiological measures of the reward-sensitivity task, LED-Levodopa negatively correlated with SCR magnitude values for non-reward stimuli in the M1 session (r = 0.49; p = 0.01). No other significant results emerged for SCR and HR measures (all ps > 0.09). For what concerns the TD task, LED-DA positively correlated with AUC values for money in the M1 session (r = 0.44, p = 0.02). Lastly, LED-DA negatively correlated with (log) K values for money in all of the three sessions (Sham: r = -0.47, p = 0.02; DLPFC: r = -0.40, p = 0.04; M1: -0.52, p < 0.01).

2.8 Discussion

Study 2 explored whether higher reward responsiveness (liking and wanting) and greater temporal discounting of rewards were present in PD+ICD patients. Moreover, it explored whether anodal tDCS over the left DLPFC could be effective in restoring such possible alterations.

Several findings emerged. As to our first aim, we found that PD+ICD exhibited higher wanting scores for reward stimuli compared to PD and C. This result is in line with studies showing an increased activity in different reward brain areas (indexed as a measure of wanting) after reward presentation in PD patients with ICD compared to controls (Napier et al., 2015). However, differently from these studies, we found also that PD+ICD showed higher liking scores compared to control groups. More in general, this result is at variance with the incentive sensitization theory (Berridge et al., 2009), according to which wanting for rewards may grow over time independently of reward liking as an individual develops compulsive reward seeking (Napier et al., 2015). Two main considerations can be advanced. First, it is possible that our explicit self-ratings fail to distinguish liking and wanting components of reward responsiveness. Indeed, several human studies have suggested that they are highly correlated, especially when using self-report measures (Pool et al.,

2016; Havermans, 2011, 2012). In addition, this difference between PD+ICD and controls in either explicit liking and wanting did not emerge when using implicit measures such as HR and SCR during the reward sensitivity task. Second, PD+ICD' altered liking may be linked with mood disturbances, since they commonly accompany the manifestation of ICD in PD (Giovannoni et al., 2000; Gatto and Aldinio, 2019).

Another interesting result of this study is that PD+ICD showed higher wanting scores also for appealing non-reward stimuli, but in this case only compared to PD. This finding might result from a higher motivation of PD+ICD subjects and/or from a reduced motivation of PD subjects, since it has been suggested that they represent opposite ends of a dopaminergic continuum, where the former and the latter are associated with hyper and hypodopaminergic state, respectively (Sinha et al., 2013; Napier et al., 2015). Our results could be taken to support also a relatively non-specific exaggerated 'wanting' of PD+ICD compared to PD (O'Sullivan et al., 2011). However, it should be mentioned that in the majority of neuroimaging studies on these patients (Evans et al., 2006; O'Sullivan et al., 2011; Voon et al., 2017), the heightened activity in reward related areas such as the ventral striatum (indexed as a measure of wanting) was specific to reward cues and not to neutral cues. As mentioned earlier, we included non-reward stimuli that were not "neutral" as the ones used in the above-mentioned studies, since they were matched with reward stimuli for several variables (e.g., arousal and valence). Therefore, it might be possible that also these stimuli resulted appealing for PD+ICD participants.

Surprisingly, we found also that LED-Levodopa positively correlated with self-ratings of wanting of non-reward stimuli, but not rewarding ones. This result might be biased by the heterogeneity of reward-related stimuli included in the study (e.g., gambling pictures and dopamine replacement therapies pictures) which might not be resulted appealing for some patients.

As to temporal discounting of rewards, we found that the PD+ICD group showed greater TD regardless of the type of reward (food or money) when comparing hyperbolic *K* values across groups. This result is in line with observations of greater temporal discounting of rewards in patients in the

general population with substance use disorders and pathological gambling (Evans et al., 2005; Pontone et al., 2006), as well as in PD patients with ICD (Voon et al., 2010; Housden et al., 2010; Leroi et al., 2013). Importantly, we showed also for the first time in the same experiment that PD+ICD patients had a greater TD compared to controls for both food (primary) and money (secondary rewards). It has been suggested that this altered temporal discounting of PD patients with ICD might results from excessive dopaminergic transmission in the orbitofrontal cortex (OFC; Cools, 2006), to which ventral striatum projects. Alternatively, it might results from altered dopaminergic transmission in the ventral striatum itself, since both studies in rats and humans suggest that this structure plays a central role in encoding information relating to delays (Cardinal et al., 2001; Pine et al. 2009). Interestingly, discounting rates were found also to correlate with dopaminergic levels measured through LED indexes, but in the opposite direction to that predicted since greater discounting rates were associated with lower levels of LED. This suggest that impulsive choices in PD patients can be modulated by dopaminergic agents. However, as mentioned earlier, our results are at variance with two previous studies showing that both LED-Levodopa and LED-DA are associated with greater (and not lower) temporal discounting in PD patients (Voon et al., 2010; Cools et al., 2003). It has been suggested that one possible explanation of different effects of exogenously administered dopamine in temporal discounting in PD may be related to individual baseline differences on endogenous dopamine levels (Voon et al., 2010). Therefore, the relationship between dopaminergic treatments and temporal discounting is more complex and further studies are needed (Napier et al., 2015).

All together these results proved that PD+ICD is characterized by heightened liking and wanting for rewards and greater temporal discounting of reward. As mentioned earlier, our findings on the reward responsiveness tasks lend only partially support to the incentive sensitization theory (Robinson and Berridge, 1993; Berridge and Robinson, 2016), according to which dopaminergic treatment in vulnerable PD patients may boosts excessive ‘wanting’ of rewards and heightens activity in reward-related brain areas such as the ventral striatum (Evans et al., 2006; O’Sullivan et al., 2011;

Voon et al., 2017), which in turn may enhance reward-related behavior that, over time, lead to the development of ICD (Antonini and Cilia, 2009; Voon et al., 2017). However, we found also an altered liking in PD+ICD patients, which might be linked with affective disturbances. Therefore, this result is more in line with other theories of addiction, as for instance the reward deficiency theory (RDS) (Bloom et al., 2000). According to this theory, addictive behaviors are characterized by a hypoactivation of brain reward pathways mediating pleasurable experience from rewards. Therefore, this altered consummatory pleasure of PD+ICD patients might emerge in order to compensate this deficiency and stimulate brain reward areas.

Importantly, like incentive salience, it is possible that the greater TD of reward in PD+ICD result from this altered dopaminergic transmission in the ventral striatum (Housden et al., 2010), since it has been shown that this structure is involved in processing information relating to delays (Pine et al., 2009; Cardinal et al., 2001). Another possible explanation is that high levels of impulsivity of PD+ICD patients could be mediated from excessive dopaminergic transmission in frontal regions, which in turn alter their reward valuation processes (Housden et al., 2010; Cools, 2006).

As to our second aim i.e. the effect of DLPFC stimulation, no effects were found on both wanting (explicit and implicit) and temporal discounting scores. However, significant effects were observed on explicit liking scores: while PD+ICD participants showed higher liking scores compared to PD in the M1 session and in the Sham session, during the DLPFC session no group differences emerged. Interestingly, liking scores for both reward and non-reward stimuli positively correlated with QUIP subscale scores for ICD (across all PD participants) in the Sham and in the M1 session. However, during the DLPFC session no significant correlations emerged.

Therefore, anodal tDCS over the left DLPFC of PD+ICD patients seems to modulate their affective/hedonic responses to appealing stimuli (for both reward and non-reward stimuli), but not their motivational responses to reward stimuli. One possible explanation for the result on self-ratings of liking is that, by targeting the DLPFC, a key brain node in the frontal-striatal network that govern executive control, the effect of anodal tDCS may be particularly evident in PD+ICD patients due to

their deficits in cognitive control (Santangelo et al., 2017). More in details, this enhanced cognitive control over affective/hedonic responses to appealing stimuli in PD+ICD could be mediated by the activity of the DLPFC over the ventromedial prefrontal cortex (vmPFC), which has been associated to the consummatory process of reward (Hare et al., 2009).

As mentioned earlier, we did not find effect of the stimulation of on both wanting (explicit and implicit) and temporal discounting scores. Although speculative at this point, it might be possible that a single session of anodal tDCS over the left DLPFC could be effective in modulating affective/hedonic responses of PD+ICD patients but not in restoring frontal-striatal circuitry abnormalities mediating their wanting and temporal discounting of rewards. Indeed, as regards motivational wanting, a recent meta-analysis on excitatory brain stimulation techniques targeting the DLPFC for reducing food and drug craving behavior has found larger effects in multi-session relative to single-session stimulations (Song et al., 2019). Also for what concerns temporal discounting rates, it may be that an individual's ability to delay gratification cannot be easily modified with a single session of tDCS (Kekic et al., 2014), particularly in subjects with impaired fronto-striatal dopaminergic functions such as PD patients (Voon et al., 2017). Another possible explanation is related to participants' baseline impulsivity. More in details, a recent study has found that participants with higher baseline impulsivity experienced lower relative change in temporal discounting tasks during tDCS over the left DLPFC (Shen et al., 2016). Therefore, the higher levels impulsivity shown in PD+ICD patients of this study and frequently reported in other studies (see Chapter 1) may explain why DLPFC manipulation did not bias PD+ICD patients' behavior.

Interestingly, we found also that higher levels of ICD are associated with a greater temporal discounting, but only when PD participants received anodal tDCS stimulation either over the DLPFC or the M1 cortex. It might be possible that these correlations emerged only during the stimulation sessions as a result of a general attention enhancement due to the effect of the anodal tDCS. Indeed, self-regulation and self-control of attention and impulsive behavior have been reported to be closely intertwined (Jackson and MacKillop, 2016; Radu et al., 2012). Moreover, in a recent study combining

anodal tDCS over the left DLPFC with PET and neuropsychological measurements it has been shown that tDCS enhances dopamine signaling in the ventral striatum and that this effect was associated with attention enhancement (Fukai et al., 2019). Similarly, a TMS study found an excitability change in M1 that was associated with the expectation of reward in a slot machine simulation task (Kapoggiannis et al., 2008), suggesting the role also of this brain area in receiving reward-related information similar to that reported for the DLFC (Pekny et al., 2015; Kapoggiannis et al., 2008).

Lastly, some limitations of the current study should be addressed. First, as regards the reward responsiveness task, we acknowledge that to have a pure measure of both liking and wanting is challenging since they are highly correlated (Berridge and Kringelbach, 2015; Pool et al., 2016). Therefore, results from the reward sensitivity task could be biased by this confound. Moreover, we included in the task pictures of dopamine replacement therapies that, however, were not matched with the other category of stimuli and were also not familiar to healthy control participants. Further analysis of the reward sensitivity task without including this set of pictures are needed. Second, we recruited PD patients with different ICD and we were interested in commonalities between these behaviors. However, differently from other studies on PD+ICD patients (O'Sullivan et al., 2011; Voon et al., 2010; Housden et al., 2010), none of the PD patients recruited reported to have gambling disorder. Therefore, our result cannot be extended also to this disorder in PD. In addition, to understand mechanistic differences, patients subgroups should be studied separately in future investigations.

In conclusion, this was the first study to examine through the use of a neuromodulation technique the role of the DLPFC in reward responsiveness and reward valuation processes in PD patients with ICD. Our results showed a greater reward responsiveness (for both liking and wanting) and a steeper temporal discounting of rewards in these patients. Moreover, results showed that tDCS may be capable to modulate the altered intensity of PD+ICD patients' liking, but not their altered wanting and temporal discounting of rewards. More broadly, these findings suggest that anodal tDCS over the left DLPFC may modulate only the affective component of their altered reward

responsiveness, and help to further understand the neural mechanisms underlying ICD in PD. Further studies are needed to explore the impact of anodal tDCS over the left DLPFC in combination with measures of reward responsiveness and reward valuation processes in PD patients with ICD.

CHAPTER 3

Diminished motivation: negative symptoms in individuals with subclinical psychotic symptoms

Study 3

Temporal and Effort cost Decision making in Healthy Individuals with Subclinical Psychotic Symptoms

[This study has been published in Terenzi et al., 2019]

Abstract

The value people attribute to rewards is influenced both by the time and the effort required to obtain them. Impairments in these computations are described in patients with schizophrenia and appear associated with negative symptom severity. This study investigated whether deficits in temporal and effort cost computations can be observed in individuals with subclinical psychotic symptoms (PS) to determine if this dysfunction is already present in a potentially pre-psychotic period. Sixty participants, divided into three groups based on the severity of PS (high, medium and low), performed two temporal discounting tasks with food and money and a concurrent schedule task, in which the effort to obtain food increased over time. We observed that in high PS participants the discounting rate appeared linear and flatter than that exhibited by participants with medium and low PS, especially with food. In the concurrent task, compared to those with low PS, participants with high PS exerted tendentially less effort to obtain snacks only when the required effort was high. Participants exerting less effort in the higher effort condition were those with higher negative symptoms. These results suggest that aberrant temporal and effort cost computations might be present in individuals with subclinical PS and therefore could represent a vulnerability marker for psychosis.

3.1 Introduction

In everyday decision-making, we are frequently asked to make decisions concerning the value of rewards. These decisions require us to take into account both the temporal cost (how long we need to wait) and the effort cost (how much effort we need to expend) to obtain a reward (Frederick et al., 2002; Botvinick et al., 2009; Zald et al., 2017; Gheza et al., 2018). Research has shown that humans devalue rewards associated with delays similarly to the way in which they devalue those associated with effort (Kable et al., 2007; Treadway et al., 2009), but that distinct brain networks respond to delayed reward and effort costs (Prévost et al., 2010; Rudebeck et al., 2006) (see Chapter 1, paragraph 1.2).

Abnormal temporal and effort discounting of rewards characterizes several forms of psychopathology, including schizophrenia (Zald et al., 2017; Culbreth et al., 2017). By and large, individuals with schizophrenia seem to choose immediate over long-term rewards more frequently than healthy controls, whether in monetary choice questionnaires (Heerey et al., 2007; 2011) or intertemporal choice tasks (Yu et al., 2017; Brown et al., 2018). Although impaired working memory has frequently been found associated with higher discounting rates (Heerey et al., 2007,2011), cognitive dysfunction alone does not seem to fully account for the abnormal discounting of rewards observed in these patients. It has been reported that patients also exhibit less willingness to work to obtain monetary rewards when a high level of effort is required, a result that has been observed across different experimental paradigms (Treadway et al., 2015; Fervaha et al., 2013). The devaluation of rewards associated with delays or effort has been found to correlate with the severity of negative symptoms, in particular avolition and anhedonia (Heerey et al., 2007; Gold et al., 2013) (but see Ahn et al., 2011 for a different result), while there is no evidence of a link with positive symptoms such as hallucinations and delusions (Heerey et al., 2011; Gold et al., 2013). Over the years, studies have shown that the increasing severity of negative symptoms corresponds to steeper temporal and effort discounting of rewards in these patients. Overall, these alterations have been associated with functional abnormalities in brain reward-related regions such as orbitofrontal and/or anterior

cingulate cortex (Gold et al., 2012, 2013), and have been interpreted as a result of a deficit in the representation of value of rewards (Waltz and Gold, 2016), especially concerning aspects such as reward prediction, anticipation and valuation. This evidence accords well with the Incentive Salience Hypothesis, proposed by Berridge, whereby the ability to experience pleasure during reward consumption (liking), and the motivation to obtain a reward (wanting or incentive salience) are two different constructs sub-served by distinct neural pathways (Berridge et al., 2009). In particular, dopamine is critical for wanting, but not liking, and plays a role in signaling incentive salience and initiating appetitive behavior (Berridge et al., 2009; Berridge and Robinson, 2016). In line with this theory, schizophrenia does not seem to be associated with diminished capacity to experience pleasure (Horan et al., 2006).

Aberrant motivation and discounting of rewards have also been observed within the psychosis continuum. For instance, steeper temporal and effort discounting of rewards has been found, although not consistently (Weatherly, 2012), in individuals with schizotypal personality traits (Li et al., 2016; Da Silva et al., 2017; McCarthy et al., 2015), while aberrant reward responsiveness has been reported in another at-risk population such as healthy individuals with subclinical psychotic symptoms (Simon et al., 2015; Papanastasiou et al., 2018). However, only a few studies on motivational processes have been conducted so far on these subjects.

The term *psychotic-like experiences* refers to subclinical psychotic symptoms experienced by healthy individuals, who, in the absence of a clinical threshold of psychosis, may share a degree of overlap in clinical manifestations with individuals with clinical psychosis (Kelleher and Cannon, 2011; Fusar-Poli et al., 2013; Modinos et al., 2010). It has been reported that these subclinical symptoms occur in about 5-8% of individuals in the general population (van Os et al., 2009; Kelleher and Cannon, 2011) and are associated with risk factors such as family risk (Lataster et al., 2009) and age (with a higher prevalence during adolescence) (Pulton et al., 2000; Hanseen et al, 2005). Studies have found that these subclinical symptoms have a low rate of transition to psychotic disorder (van Os et al., 2009). However, the exposure to additional environmental risk factors such as trauma

(Spauwen et al., 2006), cannabis use (Henquet et al., 2005) and urbanicity (Spauwen et al., 2004, 2006) can lead to poorer outcome of persistence and clinical need of care (Kelleher and Cannon, 2011; van Os et al., 2009). In terms of absolute risk, a 15-years longitudinal study has found that 25% of children with subclinical psychotic experiences at age 11 developed schizophreniform disorder at age 26 (Poulton et al., 2000). Similar findings have been reported in another independent study (Hanssen et al., 2005).

However, only few studies have investigated reward responsiveness in these individuals. Interestingly, in one study of 37 healthy participants with varying levels of subclinical psychotic symptoms it has been observed that dysfunctional activity in the ventral striatum during a task assessing anticipation of monetary gains and losses was dependent on the degree of symptom expression (Simon et al., 2015). Similar results were found in another study on 1434 healthy adolescents with different levels of subclinical psychotic symptoms. Interestingly, in this study reward responsiveness was also characterized by alterations in prefrontal function (Papanastasiou et al., 2018), thus suggesting the involvement of a broader fronto-striatal network in these alterations.

However, the above-mentioned studies in this population investigated selectively reward responsiveness without including direct measurement of reward valuation processes such as temporal and effort discounting of rewards. Since contemporary models of psychosis suggest that aberrant reward responsiveness is involved in the cause of psychotic disorders, studying these alterations in healthy individuals with subclinical psychotic symptoms may be useful for early detection and intervention (van Os et al., 2009).

In the present study we investigated whether alterations of both temporal and effort computations are present in individuals with subclinical psychotic symptoms, by using a temporal discounting task and a concurrent schedule task, which assesses the willingness to exert effort to obtain a reward. Stimuli of the concurrent task were selected according to a liking rating task that also allowed us to obtain liking scores. In the first task, we used both monetary and food rewards, while in the second task we used only food rewards. We opted for this type of reward because,

especially in the concurrent task, a primary reward such as food is best suited to disentangle the liking and wanting processes (Prévost et al., 2010). We used the Community Assessment of Psychic Experiences (CAPE) (Mossaheb et al., 2012) to identify individuals with subclinical psychotic symptoms. This self-report measure assesses the frequency and distress of psychotic-like feelings, thoughts, or mental experiences related to three domains: positive, negative and depressive symptoms. From a large sample of 334 healthy participants who were screened for psychotic-like experiences, we selected three groups based on the level of psychotic symptoms (high PS, medium PS and low PS) using cut-offs on positive symptoms provided by the CAPE (Mossaheb et al., 2012).

Based on the literature on schizophrenia patients, we hypothesized that individuals with high and/or with medium PS might choose immediate over long-term rewards more frequently compared to individuals with low PS, and to be less willing to exert effort in the concurrent schedule task. Furthermore, we expected that a steeper temporal discounting of rewards and/or a decreased willingness to expend effort to obtain rewards would be associated with negative but not positive symptoms severity.

3.2 Material and Methods

Participants

An initial sample of 334 participants, mainly students at the University of Trieste, were contacted through a social network. They filled out an internet based questionnaire assessing subclinical psychotic symptoms (CAPE) (Mossaheb et al., 2012). The CAPE is a 42-item questionnaire that measures positive, negative and depressive symptoms and it has been proved to be a reliable and valid measure for self-reported subclinical psychotic symptoms in the general population (Konings et al., 2006). From the above-mentioned sample, 60 participants were selected. The exclusion criteria were: (1) no personal history of neurological or psychiatric illness; (2) no family history of psychiatric illness in first-degree relatives; (3) no use of illicit substances (see Modinos et al., 2010), (4) no eating disorders (assessed with the Eating disorder Inventory questionnaire, EDI-3)50; and no specific food

restrictions (e.g., vegetarianism, allergy and others). All participants had a normal intelligence quotient measured using the Test di Intelligenza Breve (TIB) (Sartori et al., 1997) (mean: 106.2; SD: ±3.49; range: 95.72–112.74).

Since two CAPE cut-off scores have been proposed to identify individuals at-risk for psychosis (respectively, above 2.8 and 3.2 in the positive dimension sub-scale) and they have different levels of sensitivity, specificity, positive and negative predictive values (Mossaheb et al., 2012), in our study, we decided to use both of them and we divided participants into three groups. Specifically, 19 individuals with "high" PS, CAPE score > 3.2), 21 with "medium" PS ($2.8 \leq CAPE \leq 3.2$) and 20 with "low" PS (CAPE score < 2.8) were recruited. They were matched according to age, education and BMI. Written informed consent was obtained from all of them. All subjects were paid for their participation. The SISSA Ethics Committee approved the study, which was conducted in accordance with the Declaration of Helsinki.

Procedure

Participants were instructed to refrain from eating at least 2 hours before attending the experiment, in order to induce similar levels of hunger across subjects. Their subjective ratings of hunger were also collected, in order to control for macroscopic differences among subjects. We collected participants' weight and height, and calculated body mass index (BMI) by dividing weight in kilograms by the square of height in meters (kg/m2). Participants were asked to perform, in a random order, two temporal discounting tasks and a concurrent schedule task. At the end of the experimental session, they underwent some neuropsychological tests and completed several questionnaires.

Temporal discounting Tasks (temporal cost decision making)

Participants performed two computerized temporal discounting tasks in which they made choices between an amount of reward that could be received immediately (immediate option) and an amount of reward that could be received after some specific delays (delayed option) (Sellitto et al., 2010).

Specifically, after the presentation of a fixation cross (1 s), a choice between the immediate and the delayed option was presented. In each choice the amount of the reward, the image of the reward and the delay of delivery were displayed. Participants made their choices by pressing one of two buttons (see Fig. 3.1). After that, the chosen option remained on the screen for 1 s. The inter-trial interval was 1.5 s. Participants were asked to make five choices per block. Each block corresponded to a specific delay: 2 days, 2 weeks, 1 month, 3 months, 6 months and 1 year. An adjusting amount procedure was used across blocks to determine participants' discounting rates. More specifically, the first choice presented to participants was always between 20 units for the immediate option and 40 units for the delayed one. During the task, the delayed option remained fixed; on the other hand, the immediate option was adjusted using a staircase procedure (Myerson et al., 2003). Thus, when the immediate option was chosen, in the following choice the amount of this option was decreased by half of the difference between the delayed and the immediate option. Conversely, when the delayed option was chosen, in the following choice the amount of the immediate option was increased. The size of the adjustment of the immediate option during trials was always half of the previous adjustment. After five choices for a specific delay, the participant began a new series of choices with another delay. The subjective value for each block was estimated as the immediate amount that would have been presented on the sixth trial. In one task, we used food (primary reward) while in another we used money (secondary reward). All rewards were hypothetical. For what concerns the food task, participants were asked to choose their preferred food from a selection of six popular snacks (to increase task ecological validity, snacks usually present in the vending machines were used as stimuli).

Concurrent schedule task (effort cost decision making)

Before the concurrent schedule task, participants performed a liking-rating task in order to select food stimuli. Specifically, they were presented with eight real food items, four of which were high-calorie items (snack foods: Tuc, Kit-Kat, Kinder-Bueno and peanuts) and four were low-calorie items (fruits

and vegetables: corn, carrots, strawberry yogurt and oranges) that had been previously selected through a questionnaire filled out by an independent sample (n = 118). Participants were asked to taste each food and subsequently rate their in-the-moment liking on a 11-point line Likert scale ranging from 0 (not at all) to 10 (extremely liked). Two favorite foods, one high-calorie and one low-calorie food, which did not differ more than one point on the 11-point Likert scale, were selected as stimuli in the experimental task (for one subject the difference was two points). For a similar procedure see Giesen et al. (2010).

Following the liking-rating task, participants completed the concurrent schedule task. They were instructed that the task goal was to earn points to obtain two foods selected by the computer among those presented in the taste test. Specifically, they were asked to press a left or right key in correspondence with the part of the screen that displayed the food they wanted to earn a point for. However, they were also instructed that, as the task proceeded, it would become harder to get points for one of the two foods and that at the end of the experiment the total amount of food points obtained would be converted into the same amount of the respective food (in grams) and given to them. The task consisted of five schedules and each schedule comprises 20 choices. In the first schedule, the reinforcement ratio for both the snack option and the fruit or vegetable option was set at FR2: a point was earned every two presses on the same key for the corresponding food. The number of button presses for the snack option doubled every schedule (FR2, FR4, FR8, FR16, FR32). Thus, in the last schedule (FR32) participants were asked to press a key twice to obtain

a fruit or vegetable point and 32 times on the other response key to earn one point for snacks (see Fig. 3.2). Allocation of the images (high-calories item vs. low-calories item) to the side of the screen (left vs. right) was counterbalanced across participants. One subject did not perform this task due to technical problems.

Questionnaires and Neuropsychological tests

Participants were asked to complete the following questionnaires: the Behavioral Inhibition & Activation Scales (BIS/BAS) (Leone et al., 2001), the Temporal Experience of Pleasure Scale (TEPS) (Gard et al., 2007), the Barratt Impulsiveness Scale (BIS-11) (Fossati et al., 2001) and the Beck Depression Inventory (Beck et al., 1996). Furthermore, participants performed the following neuropsychological tests assessing working memory and executive functions: Digit Span Forward test (Orsini et al., 1987) and Stroop Color Word Test (SCWT) (Caffarra et al., 2002).

Statistical Analysis.

Data were analyzed using Statistica 8.0 (StatSoft, USA) software. Kolmogorov-Smirnov test was undertaken to demonstrate that data were normally distributed. Comparisons between groups on demographic, questionnaire and neuropsychological measures were performed using one-way analyses of variance (ANOVA). Gender distribution was analyzed using $\chi 2$ test. For temporal discounting tasks, we assessed which of three different models (linear, hyperbolic and exponential) fitted the data better by focusing on R^2 scores (Smith et al., 2008). Next, the rate at which the subjective value of a reward decays with delay was assessed through two indices: the area under the empirical discounting curve (AUC) (Myerson et al., 2001) and the slope of the regression line between subjective value and time intervals. A repeated-measures analysis of variance (ANOVA) on AUC values was performed with Task (Food/Money) as within-subjects variable and Group (high PS/medium PS/low PS) as between-subjects variable. The same analysis was performed on the slope values. In the Liking task, a repeated-measures ANOVA on rating scores was performed with type of food (high-calorie/low-calorie) as within-subjects variable and group (high PS/medium PS/low PS) as between-subjects variable. In the concurrent task, the rate at which participants are willing to work for snack foods was assessed through two indices: the number of key presses for the snack option for each schedule (FR2/FR4/FR8/FR16/FR32) and the individual slope, representing the trend of participant's effort. Comparisons between groups in this task were performed using Mann–Whitney U-test.

3.3 Results

Demographic and clinical data.

Individuals with high PS, medium PS and low PS were matched for gender, age, education and BMI (*ps* > 0.07). In addition, they did not differ significantly on subjective ratings of hunger (*ps* > 0.34). Participants with high PS and medium PS scored significantly higher than participants with low PS on all the CAPE sub-scales (all *ps* < 0.01). Compared to those with medium PS, participants with high PS scored higher on the CAPE positive and negative symptoms sub-scales (respectively, $p < 0.001$ and $p < 0.05$) but not in the depression sub-scales (all *ps* > 0.07). No differences between groups emerged when the BDI-II scale, the BIS-11, the TEPS and the BAS questionnaires were analyzed (all *ps* > 0.1). Furthermore, no differences emerged in the Digit Span forward test ($p = 0.76$) and in the Stroop Test for both performance time and number of errors (all *ps* > 0.73). For demographical and clinical information see Table 3.1. See supplementary information for detailed statistics.

	High PS (n=19)	**Medium PS (n=21)**	**Low PS (n=20)**
Gender (female)	14	16	9
Age (y)	23.47 (2.91)	23.09 (3.3)	23.75 (2.71)
Education (y)	14.05 (2.27)	14.19 (1.8)	14.55 (1.85)
BMI	23.14 (2.56)	21.82 (3.45)	21.89 (2.6)
Psychosis Proneness (CAPE):			
Positive symptoms	3.73 (0.53)* ≠	2.96 (0.12)≠	2.42 (0.2)
Positive frequency	1.88 (0.23)* ≠	1.57 (0.1)≠	1.3 (0.15)
Positive distress	1.85 (0.36)* ≠	1.39 (0.12)≠	1.12 (0.11)
Negative symptoms	4.82 (0.91)* ≠	4.25 (0.79)≠	3.4 (0.86)
Negative frequency	2.27 (0.44)* ≠	2.01 (0.35)≠	1.68 (0.37)
Negative distress	2.55 (0.52)* ≠	2.23 (0.48)≠	1.72 (0.51)
Depressive symptoms	5.22 (0.95)≠	4.69 (0.9)≠	3.77 (0.86)
Depressive frequency	2.37 (0.46)≠	2.14 (0.36)≠	1.83 (0.89)
Depressive distress	2.85 (0.56)≠	2.55 (0.6)≠	1.94 (0.54)
Cognition:			
Digit Span Forward	6.74 (1.1)	6.71 (1.06)	6.95 (1.15)
Stroop: time (s)	9.7 (5.56)	10.27 (5.07)	9.27 (5.81)
Stroop: errors	0.14 (0.42)	0.17 (0.45)	0.07 (0.24)
Mood:			

BDI-II	12.16(6.98)	10.19 (7.33)	7.35 (5.7)
Reward sensitivity/impulsivity:			
BAS total	41.48 (4)	41.19 (4.74)	41.2 (3.68)
BAS reward responsiveness	18.84 (1.26)	18.48 (1.75)	17.75 (1.68)
BAS drive	11.74 (1.88)	12.09 (2.12)	12 (2.15)
BAS fun-seeking	10.89 (2.82)	10.62 (2.4)	11.45 (1.85)
TEPS anticipatory	44.58 (4.07)	45.52 (4.61)	44.15 (5.57)
TEPS consummatory	36.47 (4.73)	37.81 (4.27)	35.4 (4.08)
BIS total	65.26 (9.46)	61.57 (9)	60 (7.75)
BIS attentional	17.58 (3.42)	17.09 (2.84)	15.8 (2.63)
BIS motor	22.42 (4)	19.9 (3.67)	20.3 (3.93)
BIS non-planning	25.26 (4.01)	24.57 (4.54)	23.9 (3.04)

Table 3.1. Demographic, neuropsychological and questionnaire data (mean and standard deviation).
*Significantly different from medium PS, $p < 0.05$; ≠significantly different from low PS, $p < 0.05$; y = years; s = seconds; BMI = body mass index; BDI-II = Beck depression Inventory; BAS = Behavioral Activation Scale; BIS = Behavioral Inhibition Scale; TEPS = Temporal Experience of Pleasure Scale; CAPE = Community Assessment of Psychic Experience.

Temporal discounting tasks

The ANOVA on AUC with Group (high PS, medium PS, low PS) x Task (food, money) yielded a significant main effect of Task ($F_{1, 57} = 8.06$, $p < 0.01$), meaning a steeper temporal discounting for food than money. No other significant results emerged (*ps* > 0.68). The comparison between linear, hyperbolic and exponential discounting models showed that the linear model fitted the data better than the other models across rewards and groups (see **Table 3.2**).

	Money			Food		
	Linear	Hyperbolic	Exponential	Linear	Hyperbolic	Exponential
High PS	0.9	0.7	0.5	0.9	0.5	0.3
Medium PS	0.8	0.9	0.6	0.9	0.8	0.5
Low PS	0.9	0.8	0.6	0.9	0.7	0.3
Overall	0.9	0.8	0.6	0.9	0.6	0.4

Table 3.2. R^2 values for Linear, Hyperbolic and Exponential model fits across rewards and groups.

The ANOVA on the slope values of the linear regression yielded a significant main effect of Task ($F_{1, 57} = 10.61$, $p < 0.01$) and a main effect of Group ($F_{2, 57} = 8.21$, $p < 0.001$). Post-hoc analysis showed a less steep slope for individuals with high PS compared to individuals with medium PS ($p < 0.01$)

and low PS ($p < 0.01$) (see **Figure 3.1).** There was no Group x Task interaction ($F_{2, 57} = 1.44$, $p = 0.24$). See supplementary information for statistics on hyperbolic parameter k.

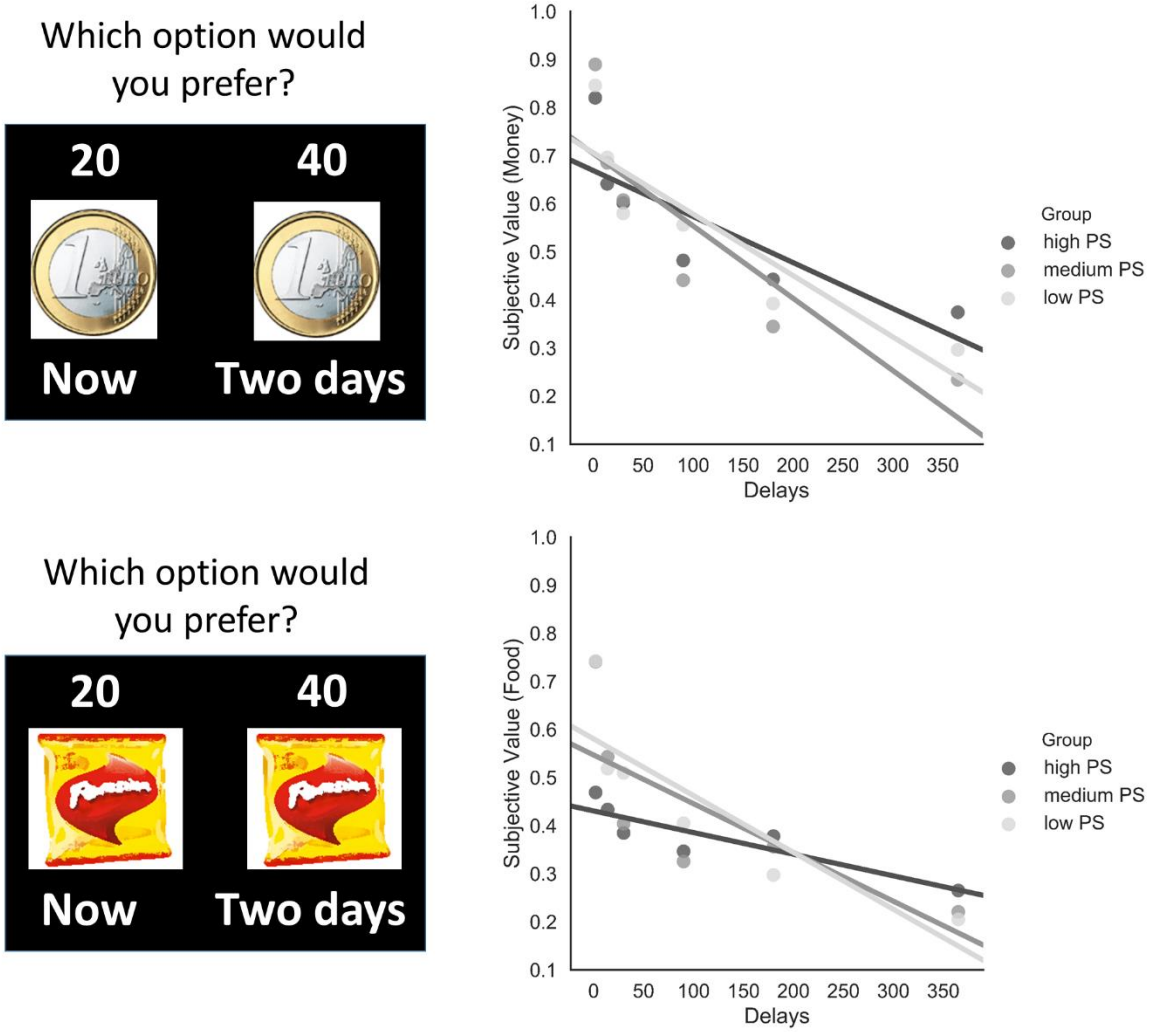

Figure 3.1. Temporal discounting tasks (left panel). Mean subjective values for money and food for high PS, medium PS and low PS (right panel). Lines represent the slope of the linear regression between subjective value and time intervals (delays).

Concurrent schedule task

The ANOVA on liking rating scores yielded a significant main effect of type of Food (F1, 57 = 24.21, $p < 0.001$), meaning a higher liking for high-calorie items than low-calorie items. No other significant results emerged (*Ps* > 0.6). During the concurrent schedule task, participants did not differ on number of key presses for the snack option in the following FR2, FR4, FR8 and FR16 schedules (all *ps* > 0.4). However, in the FR32 schedule the number of key presses was lower for the high PS group compared

to the low PS group close to being statistically significant (U = 114, Z = −1.94, p = 0.052) (see Fig. 3.2). There were no differences in this schedule between individuals with high PS and medium PS (U = 132.5, Z = −1.81, p = 0.07) and between individuals with medium PS and low PS (U = 196, Z = 0.09, p = 0.92). Furthermore, participants did not differ on slope values (all p > 0.06). See supplementary materials for detailed statistics.

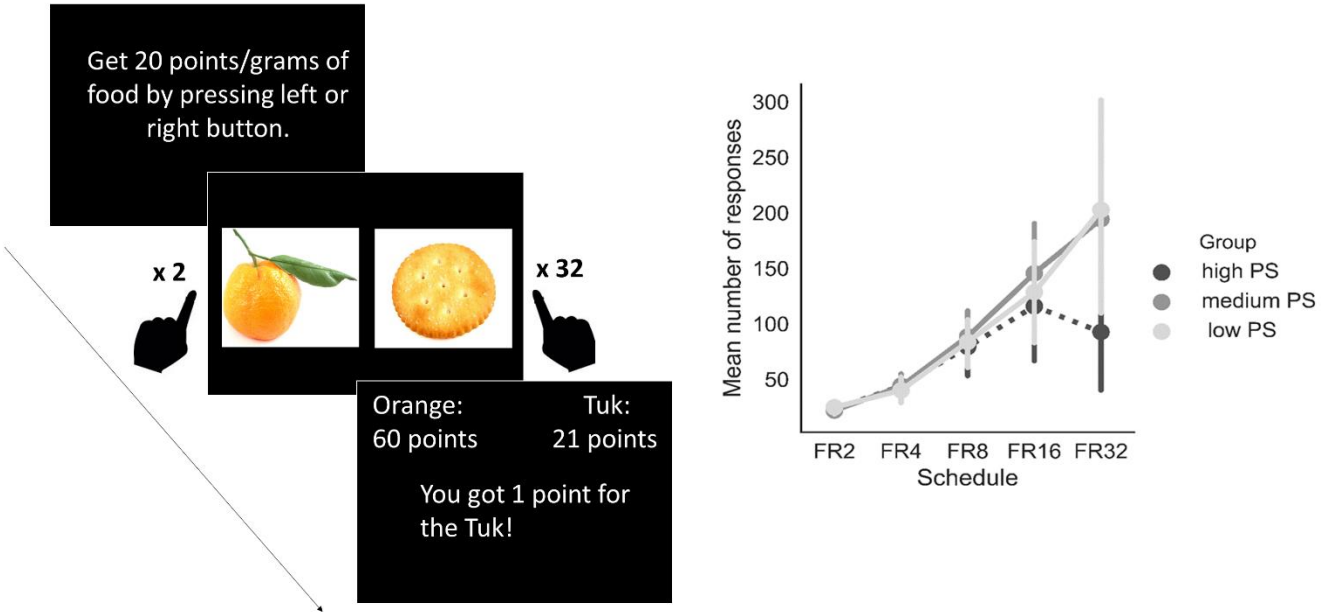

Figure 3.2. Concurrent schedule task. Example trial sequence of the FR32 schedule (left panel). Mean number of responses for snacks per schedule for high PS, medium PS and low PS subjects (right panel). FR refers to fixed ratio, which is the number of responses required to earn a single-snack point. FR for low-calorie items stay at 2 (FR2), whereas the FR for snack increases during the task (from FR2 to FR32). The error bars represent SEM. Representative images of food used in the experiment. Images have been taken from Foroni et al. (2013).

Correlation Analyses

Across all participants, *positive* symptoms positively correlated with the slope values of temporal discounting tasks for both food (r = 0.39, p < 0.01) and money (r = 0.30, p = 0.02) meaning that higher positive symptoms were associated with lower discounting of delayed rewards across time. Furthermore, participants with higher *negative* symptoms exhibited less willingness to work to obtain the snack food in the concurrent task (correlation between negative symptoms and the number of key presses for the snack option in the FR32 schedule: rho = −0.27, p = 0.04). See Fig. 3.3. In addition,

depressive symptoms and participants' effort performance in the FR32 schedule resulted inversely correlated (rho = −0.31, p = 0.01). However, this negative correlation was not statistically significant after controlling for age (rho = −0.25, p = 0.06).

For detailed correlational analyses and analyses on hyperbolic parameter k, see Table 1B (Appendix B).

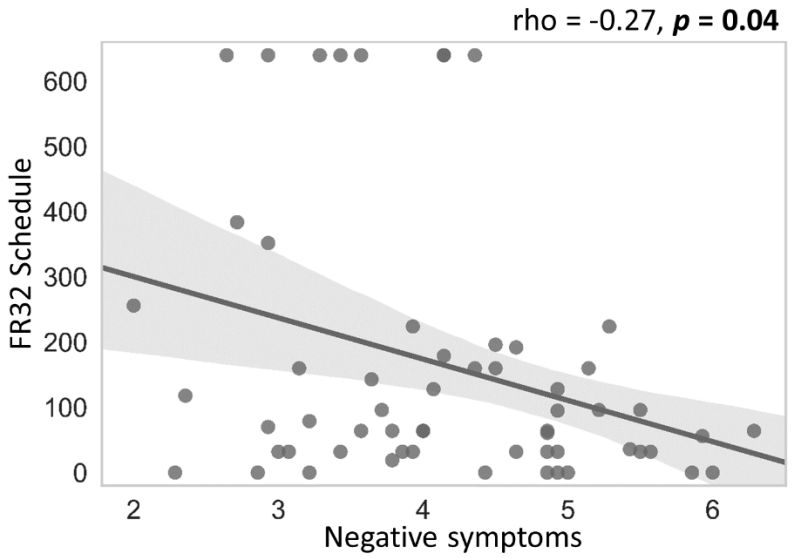

Figure 3.3.Correlation between negative symptoms and the FR32 schedule in the concurrent task.

3.4 Discussion

The goals of this study were to examine: i) whether alterations in temporal and effort discounting are present in individuals with subclinical psychotic symptoms and, if so, ii) whether such alterations are associated with the severity of the negative symptoms. We found that, *first*, individuals with high levels of subclinical psychotic symptoms exhibit altered temporal discounting compared to individuals with medium and low levels of subclinical psychotic symptoms. *Secondly*, they liked food rewards similarly to the other groups and result willing to exert the required effort to obtain them. Only when the effort required was high, individuals with high PS were different from the other groups at the trend level. Interestingly, individuals who were less willing to exert effort in the higher effort condition were those with higher levels of negative symptoms, confirming a link between negative

symptoms and effort discounting found in previous studies. Broadly speaking, these results are in line with studies showing alterations in temporal and effort computations in patients with schizophrenia (Culbreth et al., 2017; Fervaha et al., 2013; Gold et al., 2015). On the other hand, some of our findings are at variance with these studies, as well as with our expectations. First, individuals with high levels of subclinical psychotic symptoms failed to exhibit a steeper discounting rate compared to controls. Secondly, discounting computations did not correlate with the severity of negative symptoms. We discuss results concerning temporal and effort discounting below.

Individuals with high levels of subclinical psychotic symptoms did not exhibit a steeper discounting rate compared to controls when we computed the AUC values. Interestingly, when we analyzed datasets using curve fitting, we found that, even if the hyperbolic model provides a good description of the data in accordance with the literature (e.g. Myerson et al., 1995), the linear model showed overall a better fit. Interestingly, we observed that, while in individuals with medium and low PS both the linear model and the hyperbolic model fit the data well with both food and money, in individuals with high PS only the linear model provided an adequate description of the data with food rewards. When the slope discounting values were analyzed, we found that in participants with high PS the rate of discounting appeared linear, and flatter than that exhibited by participants with medium and low PS, especially with food rewards. This means that individuals with high PS were less sensitive to changes in discounting rates and temporal delays. Indeed, while medium PS and low PS individuals' subjective values decreased as time delays increased, high PS exhibit lower subjective values of rewards when time delays were short (e.g. 2 days, 2 weeks) compared to the other two groups, and these values remain in general constant as time delays increased. In addition, slope values did not correlate with negative symptoms. However, this correlation was found when we considered hyperbolic parameter k (supplementary information), an aspect that deserves future investigation. These results are only partly in line with evidence that schizophrenia patients prefer more immediate rather than delayed rewards compared to healthy controls (Heerey et al., 2007, 2011; Yu et al., 2017).

We should however mention that the results of the majority of the study on patients were based on the hyperbolic model and used monetary rewards.

Apart from these considerations, the findings concerning temporal discounting seem to suggest that even individuals with subclinical psychotic symptoms may experience alterations in the representation of value of rewards. In support of this idea, studies comparing brain structure and function in individuals with subclinical psychotic experiences and healthy controls found significant differences in grey matter volume in regions associated with reward, such as the anterior cingulate regions and insula (Chan et al., 2011) as well as reduced activity in the ventral striatum (Papanastasiou et al., 2018). However, delay discounting likely results from various psychological processes like time perception (Wittman and Paulus, 2008), working memory (Bickel et al., 2011) and intelligence (Shamosh and Gray, 2008) among others, which need to be considered in future investigations. Moreover, it is interesting to note that individuals with high PS tend to discount linearly food more than money (as the analysis on model fitting shows). As mentioned earlier, in the present study the decision to use food rewards was mainly based on the concurrent scheduled task. However, this result shows that assessing temporal and effort discounting of reward could be extremely informative, as it may be possible that in this population, individuals may be more willing to wait or exert effort for some but not for all rewards.

In examining effort computations, we found that individuals with high PS show similar liking scores for food rewards compared to individuals with medium PS and low PS, and were willing to exert the required effort to obtain them. Only when the effort required was high, high PS were different from the other groups at the trend level. The absence of a significant difference between groups across the whole task may be driven by the characteristics of the task we used, in which temporal confounds are not excluded (see Chong et al., 2017). Future studies should use a more valid version of the effort task, maybe extending observations also to cognitive effort. Physical and cognitive effort have been found to share a common network of areas, such as the dorsolateral prefrontal cortex among others (Chong et al., 2017, 2018) and patients with schizophrenia have been

found to be less likely to select a hard task (either physical or cognitive) associated with a large reward compared to an easy task associated with a smaller reward (Culbreth et al., 2018).

Although this difference did not reach statistical significance, it may suggest that some alterations in effort may be present in individuals with subclinical psychotic experience. Specifically, this finding seems to suggest that anticipatory but not consummatory pleasure may be altered in individuals with subclinical psychotic symptoms. This is in agreement with results observed in schizophrenia patients showing that patients' self-reported levels of pleasure are similar to those of healthy controls when experiencing pleasurable activities (Cohen and Minor, 2010); but, unlike healthy controls, they are less likely to select a hard task associated with a large reward compared to an easy task associated with a smaller reward (Culbreth et al., 2018). Not only was our result marginally significant, but we did not observe difference between groups in anticipatory pleasure when we analyzed the results of the TEPS, a questionnaire developed to address anticipatory and consummatory pleasure in schizophrenia (Gard et al., 2007). However differences between anticipatory and consummatory pleasure have not always been observed in schizophrenia patients (Da Silva et al., 2017; Schlosser et al., 2014; Strauss et al., 2011), this suggests that future studies should investigate effort computations in individuals with subclinical psychotic experience employing multiple valid measures of effort. Moreover, since different profiles or sub-types of psychosis can be identified, with patients often showing a prevalence of either positive or negative symptoms, it would be interesting in the future to assess temporal and effort cost decision making in both sub-types enrolling a larger sample of participants.

As a final remark, we found that alterations in reward processing were present only in individuals identified with the higher CAPE cut-off score. As pointed out in the Materials and Methods section, differences exist between the two cut-offs, in that they have different levels of sensitivity, specificity, and positive and negative predictive values (Mossaheb et al., 2012). Our study suggests that using the higher cut-off is preferable, especially since it is also the one with the higher

specificity and low number of false positives (Mossaheb et al., 2012), although further research is needed.

Lastly, some limitations of the current study should be addressed. First, as we mentioned earlier, despite the usefulness of concurrent schedule task has been widely proven in animal research, this task has the disadvantage that effort costs may be confounded by temporal costs. In the present study, correlational analyses did not show any significant association with the temporal discounting task (see supplementary Table 2B); nevertheless, future studies should carefully control for this aspect. Another limitation of the current study refers to the use of the CAPE cut-offs. Cut-off values are indeed calculated on the positive dimension and do not take into account negative scores (Mossaheb et al., 2012). However, we must acknowledge that the CAPE positive symptoms subscale has been shown to detect psychotic experiences and predicts psychotic illness better than the whole 42-item scale (Mark and Toulopoulou, 2016).

In conclusion, our results are (at least in part) in line with studies conducted with schizophrenia patients, and extend current knowledge by showing that aberrant temporal and effort discounting of rewards are observed in healthy individuals with subclinical psychotic symptoms and therefore might be a vulnerability marker for psychosis. Identifying vulnerability markers for psychosis is of fundamental importance for early detection and treatment of psychosis.

Study 4

Behavioral and electrophysiological markers of altered motivation in individuals with subclinical psychotic symptoms

Abstract

In this study we aimed to replicate our previous findings showing altered temporal and effort discounting of rewards in individuals with subclinical psychotic symptoms (PS), and, explored whether resting left frontal alpha asymmetry (LFA, an electrophysiological index of motivation and impulsivity) may be a biomarker of altered motivation in these subjects.

Forty participants, divided into two groups based on the severity of PS (high and low), performed a temporal discounting tasks with food rewards and an effort-based decision making task, which combined a concurrent schedule paradigm with the use of an hand-held dynamometer. As regards the temporal discounting task, results were similar to those shown in the previous study, whereas in the effort-based decision making task no group differences emerged. LFA was found to be significantly associated with the willingness to exert effort in the hardest schedule of the effort-based task for high PS individuals but not for those with low PS.

These results suggest that aberrant temporal and effort cost computations might be present in individuals with subclinical PS. The LFA results suggest also an higher sensitivity to the cost of effort in these subjects, providing a possible electrophysiological correlate of their altered reward valuation.

3.5 Introduction

In our previous study we found that altered effort and temporal cost computations might be present in individuals with subclinical psychotic experiences (Terenzi et al., 2019). In brief, in the temporal discounting task participants with high PS show a constant subjective value as time delay increases, which means that they are not sensitive to changes in discounting rates and temporal delays,

while in the concurrent schedule task they show a reduced willingness to work to obtain rewards when the required effort is high. Importantly, participants exerting less effort in the higher effort condition are those with higher negative symptoms.

Based on these results, in the present study we aimed to replicate our previous findings showing altered effort and discounting computations in individuals with subclinical psychotic symptoms and to investigate their neuroimaging correlates through the use of the electroencephalogram (EEG).

Several studies have linked asymmetric resting state alpha band in frontal regions and in particular a greater left compared to right frontal alpha activity, also known as left frontal asymmetry (LFA), with motivation and impulsivity (see Harmon-Jones and Gable, 2018 for a review).

For instance, it has been observed that LFA modulates the propensity to engage in motivated behavior measured through self-report measures (e.g., the Behavioral Inhibition & Activation Scale - BIS/BAS; Carver and White, 1994) as well as experimental tasks (e.g., verbal memory tasks under incentive conditions; Pizzagalli et al., 2005; Coan and Allen, 2004). A similar result has been shown also using effort-based decision making tasks (Hughes et al., 2014), in which greater resting LFA predicted an increased willingness to exert effort to obtain larger rewards. It has been proposed that this functional role of LFA in approach motivation may be due to asymmetric dopamine D2/D3 receptor binding capacity in striatal and frontal brain regions (Tomer et al., 2014). In line with this hypothesis, Wacker et al. (2013) found that the association between LFA and approach motivation measured through the BAS scale (Carver and White, 1994) was attenuated following D2 receptor blockade.

Moreover, studies have linked resting alpha asymmetry not only with approach motivation but also with risk taking behavior and impulsivity traits, despite none of them has employed a discounting task. For instance, subjects with higher activity in frontal areas in the left hemisphere have been shown to display more risk proneness in risk taking tasks such as the Iowa Gambling task

(Balconi and Finocchiaro, 2015; Black et al., 2014). Conversely, subjects with higher activity in the right hemisphere show more risk aversion behavior in a risk task (Gianotti et al., 2009).
These studies suggest that LFA may be a neural indices of motivation that helps individuals overcome the effort and risk related costs of reward valuation processes (Hughes et al., 2014).

Notably, resting state EEG studies focusing on LFA in patients with Schizophrenia, have found a diminished LFA and an increased withdrawal motivation in patients relative to healthy controls, although asymmetry scores have been not found to be associated with motivational scores or negative symptoms (Horan et al., 2014; Jetha et al., 2009). Across the psychosis continuum, a reduced LFA has also been found in individuals with first episode psychosis as well as in on study on youth at clinical high risk for psychosis (Bartolomeo et al., 2019). These evidences accord well with the hypothesis that schizophrenia is associated with impairments in reward valuation processes (Fervaha et al., 2013; Brown et al., 2018) and that these impairments can be present also at earlier stages of the disease (van Os et al., 2009; Papanastasiou et al., 2018; Terenzi et al., 2019). At the same time, no studies to date have investigated the association between LFA and impulsivity in patients with Schizophrenia and across the psychosis continuum.

Based on the literature reviewed so far and on our previous study, we decided to explore whether altered effort and temporal cost computations in individuals at risk of psychosis result associated with resting frontal alpha asymmetry. Importantly, compared to the previous study, we decided to modify our experimental tasks. As described in details in the method section (paragraph 3.6), for what concerns the TD task, we used only food rewards and changed time delays from days/months to hours (with a maximum of 15 hours) in order to increase the task ecological validity. For what concerns the effort cost decision making, we employed an effort-based decision making task which combined a concurrent schedule paradigm with the use of an hand-held dynamometer (Bonnelle et al., 2015, 2016; Chong et al., 2016), in order to exclude temporal confounds (Prévost et al., 2010; Chong et al., 2016, 2017).

3.6 Materials and Methods

Participants

An initial sample of 368 participants was contacted through a social network and asked to fill out an internet based version of the CAPE (Konings et al., 2006). From this sample, 40 participants were selected. Participants had to fulfill inclusion criteria described for our previous study (Terenzi et al., 2019). In addition, all participants had a normal intelligence quotient measured using the Test di Intelligenza Breve (TIB, Sartori et al., 1997) (mean: 104.88; SD: ±2.92; range: 98.50–111.29). Participants were divided into two groups based on CAPE proposed cut-off score (using a score > 3.2 in the positive dimension) (Mossaheb et al., 2012). Specifically, 20 individuals with "high" PS, CAPE score > 3.2) and 20 with "low" PS (CAPE score < 2.8) were recruited. They were matched according to age, education and BMI (see Table 3.3). All participants gave written informed consent to participate in the study that was approved by SISSA Ethics Committee.

Procedure

As in Study 3, participants were instructed to refrain from eating at least for 2 hours preceding the experiment and we collected their subjective ratings of hunger and fasting. Participants' weight and height were also collected and body mass index (BMI) was then calculated. At the beginning of the experimental session, participants performed some neuropsychological tests and completed several questionnaires. They were then asked to undergo a resting state EEG recording session. Lastly, they performed, in a random order, one temporal discounting task and one effort-based task.

Temporal-discounting task

Participants performed a computerized temporal discounting task in which they made choices between an amount of food reward that could be received immediately (immediate option) and an amount of food reward that could be received after some specific delays (delayed option) (see Fig 3.5). We used a similar procedure to that used in Study 3. The task included 4 choices per block. Each

block corresponded to a specific delay: 1 hour, 2 hours, 5 hours and 15 hours. One subject did not perform this task due to technical problems.

Effort-based decision making task

Before this task, as in the previous study, participants performed a liking-rating task in order to select two favorite foods (equally liked), one high-calorie and one low-calorie, as stimuli in the experimental task. Following the liking-rating task, participants performed the effort-based decision making task. This task consisted of making a series of choices that were related to different physical effort costs demands. Participants were instructed that they had to earn points to obtain the two favorite foods selected before by pressing a left or right key in correspondence with the part of the screen that displayed the food they wanted to earn a point for. Immediately after the decision, they were asked to maintain a constant contraction of force for 14 sec through a hand-grip dynamometer in order to get 1 point/gram of the selected food. Importantly, they were also instructed that the amount of force required would increase during the task. More in details, the task consisted of three schedules of 15 choices, meaning that a total of 45 points/grams of food had to be earned and the eaten after the task. In the first schedule (*easy schedule*), the proportion of force to maintain constant to get 1 point/gram of both food options was equal to the 8% of the participant's maximal voluntary contraction (MVC). In the following two schedules (*medium and hard schedules*), the amount of effort required for the fruit/vegetable option was kept at the 8% while the force associated with the choice of the snack option increased (13% and 33% in the medium and hard schedule, respectively). Thus, in the hard schedule participants were asked to decide if they were willing to maintain a constant contraction corresponding to the 33% of their MVC if they wanted to get 1 point for the snack option or to exert a lower amount of effort (8% of MVC) if they choose to get 1 point for the fruit/vegetable option. In each trial participants were presented with a real-time feedback on their force. To ensure that participants were able to maintain a constant contraction of effort at each different schedule of force

they were asked to perform a training session before the experimental task. See Fig 3.6. For a similar procedure see Chong et al. (2017) and Giesen et al. (2010).

EEG data acquisition and analysis

We used EEG procedures commonly employed in studies in which resting state FAA is measured (Allen et al., 2004). Particularly, continuous EEG signals were recorded with 64 channel BioSemi ActiveTwo system (BioSemi Inc., Amsterdam, Netherlands) at a sampling rate of 1024Hz. A Common Mode Sense (CMS) active electrode was used as the reference, and a Driven Right Leg (DRL) passive electrode was used as the ground. Two external electrodes placed on the right and left of the outer canthi, and one external electrode placed under one eye were used to obtain horizontal and vertical electrooculograms (EOG).Two additional electrodes were placed on the left and right mastoids. Individual electrode offsets were kept between ±50 μV.

EEG was recorded for 7 minutes in total, divided into two different sessions of 3.5 minutes each (one session with eyes closed and one with eyes open), which were administered in a counterbalanced order across participants. Data were preprocessed offline with EEGLAB 14.1.2b (Delorme and Makeig, 2004), implemented in Matlab R2017b.

EEG signal was re-referenced to the average of mastoids and filtered with a bandpass at 1-40 Hz. Further, bad channels were removed through an automatic procedure as implemented in EEGLAB (Delorme and Makeig, 2004) and an independent component analysis (ICA) was computed to remove eye and muscle artefacts. The power spectrum (μV2/Hz) in the alpha range (8-13Hz) was then calculated using a Fast Fourier transformation with a 2 sec length of Hamming window, providing an index of the mean alpha power density. In addition, alpha range was divided into low (8-10 Hz) and high (10-13 Hz) alpha power in order to examine the contributions of high and low alpha separately. In order to normalize the distribution of alpha power densities values, a natural log transformation (ln) was applied (Gasser et al., 1982). EEG alpha asymmetry index (Pivik et al., 1993) was obtained by measuring the difference of log transformed alpha for homologous left and right pair of electrodes

(i.e., ln[Right] – ln[Left]). We examined electrodes F4 & F3 usually investigated in frontal asymmetry literature (Thibodeau et al., 2006; Reznik and Allen, 2018). We also included in our analysis frontal alpha values at the medial C4 & C3 and the parietal P4 & P3 electrodes (Heller et al., 1998; Horan et al., 2014). See Figure 3.4. Finally, for additional exploratory analyses (see Supplementary data) we extracted delta, theta, alpha and beta relative power frequencies by averaging signals from whole-head EEG electrodes (Fuggetta et al., 2014; Howells et al., 2018). Resting state EEG was not recorded in two subjects due to technical problems.

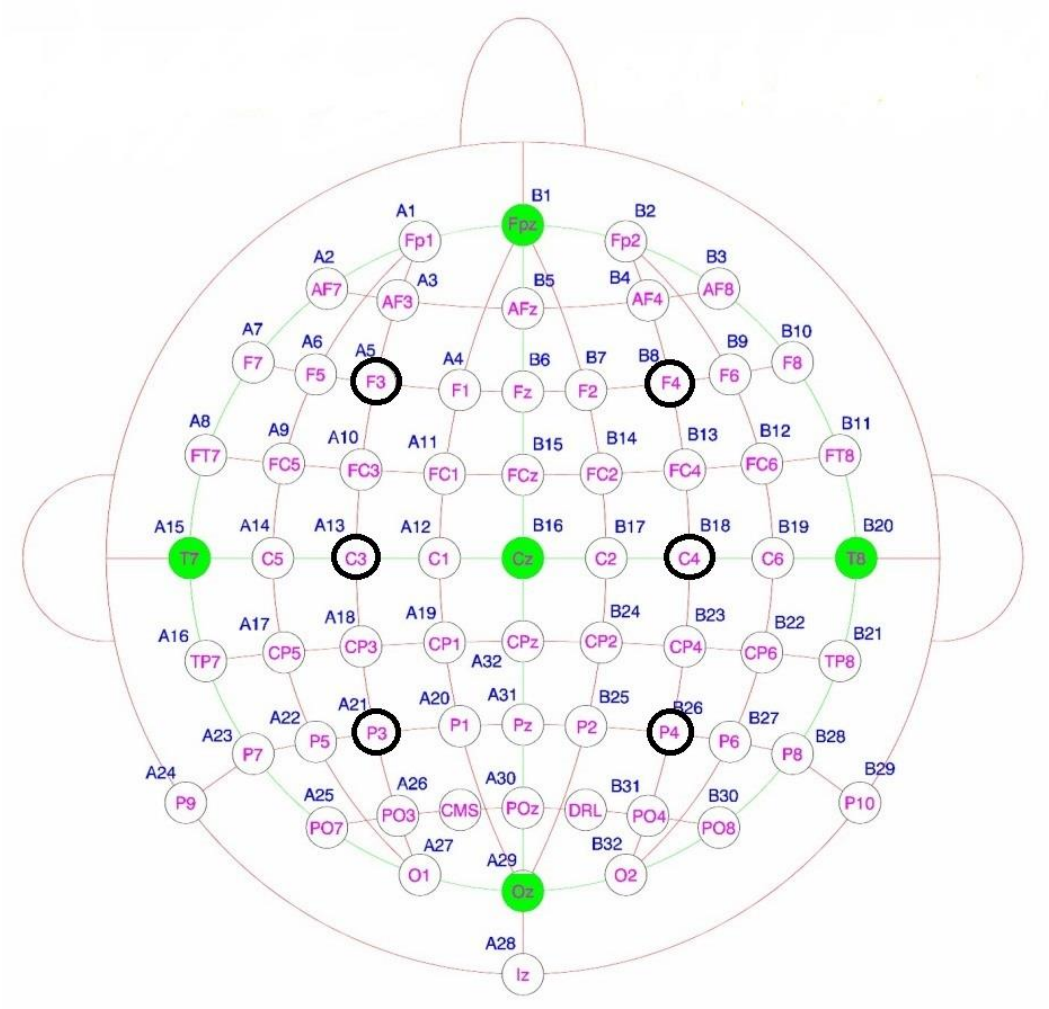

Figure 3.4. EEG electrodes. The bold circles indicate the electrodes used to compute alpha asymmetry.

Questionnaires and neuropsychological tests

Participants were asked to complete the following questionnaires: the Temporal Experience of Pleasure Scale (TEPS) (Gard et al., 2007) and the Beck Depression Inventory (Beck et al., 1996). Furthermore, they were asked to perform the Digit Span Forward test (Orsini et al., 1987) in order to assess their working memory.

Statistical analysis

Data were analyzed using Jamovi software 0.9.5.12. Parametric and non-parametric tests were used where appropriate. Kolmogorov-Smirnov test was undertaken to demonstrate that data were normally distributed. We compared groups (high PS and low PS) on demographic, neuropsychological and questionnaire measures. For the temporal discounting task, we compared the two groups in their subjective values for rewards at each time delay. Next, we assessed which of three different models (linear, hyperbolic and exponential) fit the data better by focusing on R^2 scores (Smith et al., 2008). Moreover, we calculated the area under the empirical discounting curve (AUC) as a model-free parameter (Myerson et al., 2001). In the Liking task, rating scores were compared across groups. In the effort-based decision making task, the rate at which participants were willing to work for food was represented by the percentage of the number of choices of effort exertion for the high-calorie food at each schedule (easy, medium and hard schedule). To control for the effect of fatigue in effort-based decision making tasks (Chong et al., 2015), tiredness ratings were used as covariate. For what regards the EEG measures, asymmetry scores from frontal, medial and posterior electrodes were computed and compared across groups. Parametric Pearson correlations were used to examine the relationship between demographic, questionnaire, neuropsychological, behavioral and EEG measures. Importantly, BDI scores were used as covariate in all of the above mentioned analyses in order to control for emotional status (Culbreth et al., 2017).

3.7 Results

Demographic and clinical data

Individuals with high PS and low PS were matched for gender, age, education and BMI (*ps* > 0.15). In addition, they did not differ significantly on subjective ratings of hunger ($p > 0.19$). Participants with high PS scored significantly higher than participants with low PS on all the CAPE sub-scales (all *ps* < 0.001) and on the BDI-II scale ($p = 0.01$). No differences emerged in the Digit Span forward test ($p = 0.44$). For demographical and clinical information see Table 3.3. See supplementary information for detailed statistics (Appendix B).

	High PS (n=20)	**Low PS (n=20)**
Gender (female)	18	16
Age (y)	22.9 (2.57)	22.7 (1.87)
Education (y)	13.1 (1.71)	13.9 (1.71)
BMI	22.48 (6.33)	22.56 (2.39)
Psychosis Proneness (CAPE):		
Positive symptoms	3.54 (0.29)***	2.35 (0.19)
Positive frequency	1.79 (0.23)***	1.22 (1.12)
Positive distress	1.74 (0.2)***	1.13 (0.09)
Negative symptoms	4.32 (0.9)***	3.21 (0.63)
Negative frequency	2.02 (0.34)***	1.59 (0.27)
Negative distress	2.30 (0.59)***	1.62 (0.38)
Depressive symptoms	5.24 (0.91)***	3.8 (0.77)
Depressive frequency	2.39 (0.43)***	1.83 (0.32)
Depressive distress	2.84 (0.53)***	1.62 (0.38)
Cognition:		
Digit Span Forward	6.25 (0.85)	6.45 (0.76)
Mood:		
BDI-II	14.2 (8.36)**	6.85 (4.76)
Reward sensitivity – impulsivity:		
TEPS anticipatory	42.05 (4.9)	43.95 (6.64)
TEPS consummatory	39.8 (4.53)	40 (3.64)

Table 3.3. Demographic, neuropsychological and questionnaire data (mean and standard deviation).
*p < 0.05; ** p < 0.01; *** p < 0.001; BMI = body mass index; BDI-II = Beck depression Inventory; TEPS = Temporal Experience of Pleasure Scale; CAPE = Community Assessment of Psychic Experience.

Temporal discounting task

Kruskal-Wallis ANOVAs on subjective values at each time delays with group (high PS, low PS) as a factor showed no significant differences (*ps* > 0.32; see supplementary materials for detailed statistics). A Friedman ANOVA conducted on low PS participants' subjective values across time delays showed a significant result (x^2 = 14.2 p < 0.01). Wilcoxon paired comparisons showed that subjective values were statistically different for delays that were more distant in time: from 1hour to 5 hours (p < 0.01) and 15 hours (p < 0.01), as well as from 2 hours to 15 hours (p = 0.04); while no differences emerged between subjective values that were close in time delays, such as from 1 hour to 2 hours (p = 0.09), from 2 hours to 5 hours (p = 0.20) and from 5 hours to 15 hours (p = 0.59). See Figure 3.5. The same analysis on high PS participants yielded no significant results. A one-way ANCOVA on AUC values (controlling for BDI) with group (high PS, low PS) as a factor yielded no significant results ($F_{1, 36}$ = 0.09, p = 0.76).

The comparison among linear, hyperbolic and exponential discounting models showed that the linear model fitted the data better than the other models across groups (see Table 3.4).

A one-way ANCOVA on slope values (controlling for BDI) with group (high PS, low PS) as a factor yielded no significant results ($F_{1, 36}$ = 0.12, p = 0.73).

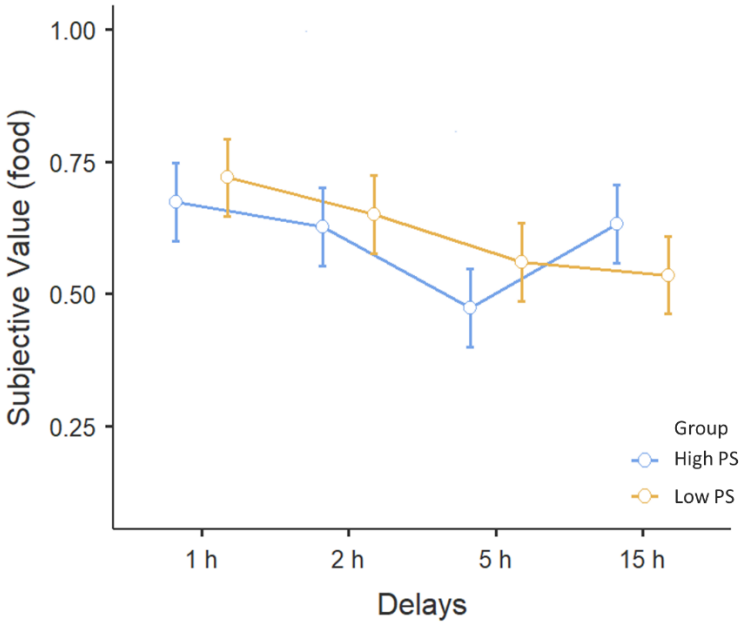

Figure 3.5. Temporal discounting tasks (left panel). Mean subjective values for money and food for high PS, medium PS and low PS (right panel). The error bars represent SEM.

	Linear	Hyperbolic	Exponential
High PS	**0.94**	0.59	0.34
Low PS	**0.98**	0.79	0.65
Overall	0.96	0.69	0.49

Table 3.4. R^2 values for Linear, Hyperbolic and Exponential model fits across groups.

Effort-based decision making task

A repeated-measure ANCOVA (controlling for BDI) on liking-ratings with Food (fruits/vegetables, snacks) a within-subjects variable and Group (high PS, low PS) as a between-subjects variable yielded no main effect of Group ($F_{1, 37} = 0.05$, $p = 0.81$) nor of type of Food ($F_{1, 37} = 0.52$, $p = 0.47$) and no interaction Group x Food ($F_{1, 37} = 1.33$, $p = 0.26$).

A repeated-measures ANCOVA (controlling for BDI and tiredness) on the percentage of choices for snack food with Schedule (easy, medium, hard) as a within-subjects variable and Group (high PS, low PS) as a between-subjects variable yielded no main effect of group ($F_{1, 36} = 0.16$, $p = 0.69$) nor of Schedule ($F_{2, 72} = 0.25$, $p = 0.78$) and no interaction Group x Schedule ($F_{2, 72} = 0.50$, $p = 0.61$). See Figure 3.6

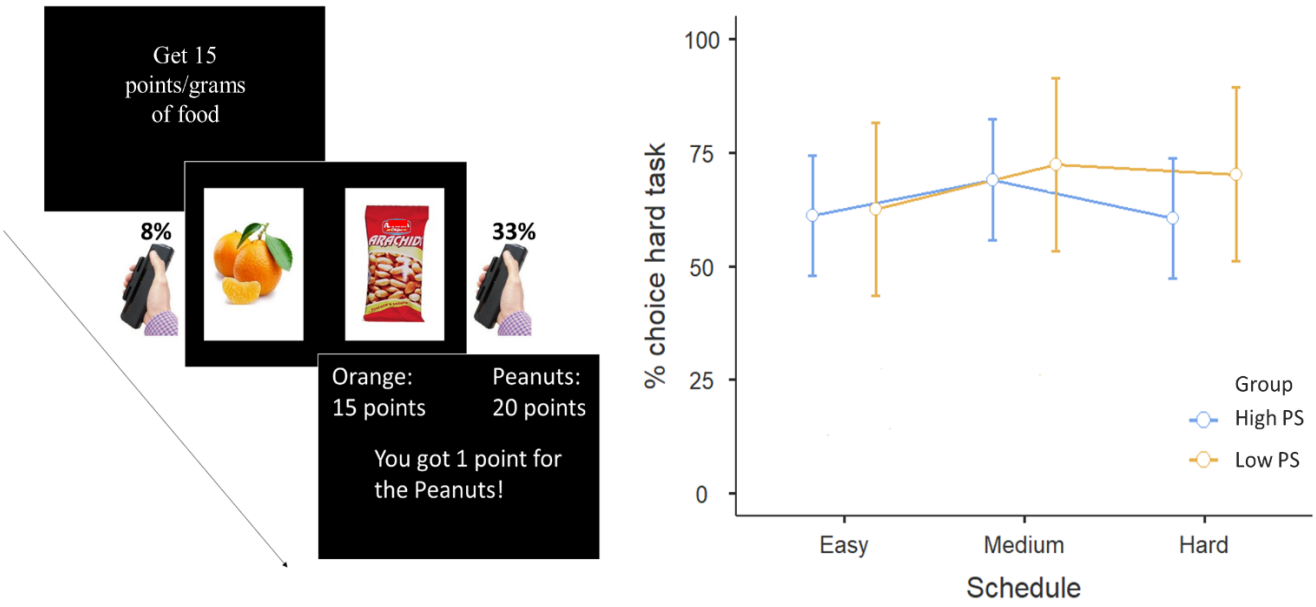

Figure 3.6. Effort-based decision making task. Example trial sequence of the hard schedule (Left panel). Mean number of % of choice for snacks per schedule for high PS and low PS subjects (Right panel). Easy, medium and hard refer to the % of force to hold for 14 sec in order to earn a single food point. The amount of force for low-calorie items stays at 8% of participants' MVC, whereas the % of force for snack increased during the task (from 8% in the easy schedule to 33% in the hard schedule). The error bars represent SEM.

EEG alpha asymmetries

A one-way ANCOVA (controlling for BDI) on asymmetry scores F4-F3 low alpha yielded no significant results ($F_{1, 35}$ = 0.28, p = 0.60). No significant results emerged also for the following asymmetry scores: F4-F3 high alpha ($F_{1, 35}$ = 0.14, p = 0.71); P4-P3 low alpha ($F_{1, 31}$ = 2.48, p = 0.13); P4-P3 high alpha ($F_{1, 31}$ = 0.40, p = 0.53), C4-C3 low alpha ($F_{1, 28}$ = 0.69, p = 0.41); C4-C3 high alpha ($F_{1, 29}$ = 2.21, p = 0.15).

Correlation analyses

No significant correlations were found between questionnaires (CAPE and TEPS) and experimental tasks and asymmetry scores (see supplementary tables 3B-3E, Appendix B). For what regards correlation analyses between experimental tasks and asymmetry scores, no significant results emerged across all subjects (see Table 3.5 and Table 3.6). However, there was a positive correlation for high participants between their % of choices of snack foods in the hard schedule of the effort-

based task and their low alpha LFA values (r = 0.59; p = 0.008). Moreover, there was a negative correlation for low PS participants between their temporal discounting slope values and their low alpha asymmetry scores derived from medial electrodes (r = -0.57; p = 0.03). See Table 3.5 and Table 3.6 for correlation analyses between experimental tasks and asymmetry scores.

	% medium choice			**% hard choice**		
	All subjects	High PS	Low PS	All subjects	High PS	Low PS
Low alpha (F4-F3)	0.25	0.40	0.07	0.28	**0.59***	0.03
High alpha (F4-F3)	0.20	0.34	0.05	0.17	0.45	-0.05
Low alpha (C4-C3)	0.16	0.07	0.11	0.48	0.48	0.22
High alpha (C4-C3)	0.18	0.08	0.30	0.04	0.04	0.18
Low alpha (P4-P3)	0.00	0.11	-0.14	-0.13	-0.06	-0.26
High alpha (P4-P3)	-0.16	0.05	-0.47	-0.27	-0.03	-0.55

Table 3.5.. Correlations between alpha asymmetry scores derived from frontal, medial and posterior electrodes and % of choices for the snack option across schedules (medium and hard) and groups (high PS and low PS). *p < 0.05.

	Slope value		
	All subjects	High PS	Low PS
Low alpha (F4-F3)	0.13	0.11	-0.46
High alpha (F4-F3)	-0.04	0.15	-0.31
Low alpha (C4-C3)	-0.06	0.22	**-0.57***
High alpha (C4-C3)	0.26	0.38	0.25
Low alpha (P4-P3)	-0.03	0.09	-0.28
High alpha (P4-P3)	-0.14	-0.11	-0.05

Table 3.6.. Correlations between alpha asymmetry scores derived from frontal, medial and posterior electrodes and Slope values of temporal discounting across groups (high PS and low PS). *p < 0.05.

3.8 Discussion

Study 4 explored whether aberrant temporal and effort discounting of rewards and abnormal EEG biomarkers of motivation were present in individuals with subclinical psychotic symptoms.

We confirmed that individuals with high PS exhibit altered temporal discounting of rewards relative to individuals with low PS: they appear not sensitive to the cost of time and showed a linear and flatter discounting rate than that exhibited by participants with low PS. Indeed, only low PS participants discounted food rewards when comparing their subjective values across time delays, while no significant differences emerged in the high PS group. In examining associations between LFA and slope values of temporal discounting tasks, no significant results were found. However, we observed that alpha asymmetry scores at medial electrodes (C4-C3) of participants with low PS were negatively correlated with their slope values, while no significant correlations emerged for the high PS group. This means that the greater the impulsivity of low PS participants (indexed via EEG asymmetry scores at central electrodes) the steeper their discounting of rewards. Even if previous studies have shown an association between alpha asymmetry scores and behavioral measures of impulsivity in healthy participants (Balconi and Finocchiaro, 2015; Gianotti et al., 2009), none of them report such result for medial electrodes. Since in our study these electrodes were located on the top of the primary somatosensory cortex, in the postcentral gyrus of the parietal lobe (Koessler et al., 2009), we may speculate that they could be involved in representing patterns of emotional/affective states, which have been found to be involved in decision making processes (Damasio, 1994; Bechara, 2005) and that these aspects may result altered in individuals with high PS (Tully and Niendam, 2014; Cohen et al., 2012). However, further studies are needed in order to better understand the meaning of this association and its absence in individuals at high risk of psychosis, especially because this is the first study that has investigated the electrophysiological correlates (via EEG cortical alpha asymmetry) of temporal discounting of rewards.

Differently from our previous study, no differences emerged in the effort-based decision making task between the two groups of participants and we did not find a significant correlation between negative symptoms and the willingness to exert effort for the snack in the hard schedule. Several considerations can be advanced. *First*, participants with high PS in this study had lower negative symptoms scores (mean ± SD: 4.32 ± 0.90) compared to those reported in high PS participants of our previous study (mean ± SD: 4.82 ± 0.91). Therefore, it may be possible that in the present study this reduced severity of negative symptoms did not allow to observe neither group differences between high and low PS participants nor the relationship between the willingness to exert effort and the severity of negative symptoms.

Second, it is possible that the high and low calorie food selected for each participant during the liking-rating task and subsequently employed in the effort-decision making task were not really equally liked. Indeed, even if participants tasted each food, their evaluation of liking was still based on a self-report measure, which could not be a reliable measure of liking (Pool et al., 2016). The observation that both high PS and low PS participants preferred to work more for the high calorie food since the beginning of the task (in the easy schedule) may confirm this speculation.

Third, participants in this task were instructed to obtain 45 points/grams of food in total, which were fewer compared to the 100 points/grams of the concurrent schedule task in our previous study. It is possible that once they decided to work more for the high-calorie food in the easy schedule they then continued to work for this food also in the other schedules in order to maximize the amount of grams of it. Thus, we cannot exclude the possibility that our task failed to capture eventual effort discounting of rewards.

Even if no differences emerged at a behavioural level, we observed interesting results on the EEG measures. Only individuals with high PS, but not those with low PS, displayed a positive correlation between LFA and the willingness to exert effort to obtain rewards in the hardest schedule of the effort-based decision making task. The lower was the effort exerted to get the reward in the hard schedule, the less high PS participants showed approach motivation (indexed via a lower LFA).

These results seem to suggest that, although both groups of participants did not show the expected discounting of rewards as effort increased across schedules, the effort employed in the hard schedule represented a real cost for high PS participants but not for those with low PS. Interestingly, it has been proposed that an increased frontal activity during reward anticipation in individuals at ultra-high risk for psychosis (Juckel et al., 2012), as well as in healthy individuals with high PS, may serve as a compensatory frontal executive process which prevent the evolution of clinically relevant psychotic symptoms (Papanastasiou et al., 2018). Based on this idea, we may speculate that individuals with high PS may have an enhanced neural sensitivity in frontal areas (asymmetry derived from frontal F4-F3 electrodes) to the cost of the effort in the decision making process and that this sensitivity might result from the above mentioned compensatory mechanisms. Further neuroimaging studies are needed using techniques (e.g., fMRI) with a greater spatial resolution in order to test this hypothesis.

As a finally remark concerning resting EEG alpha asymmetry values, no group differences emerged for frontal, medial and posterior electrodes as well as no correlations between LFA and the severity of negative symptoms. These findings are in part in line with one recent study on individuals at clinical high risk for psychosis in which no group differences in LFA emerged as well (Bartolomeo et al., 2019), suggesting that individuals at earlier stages of the psychosis continuum do not have different EEG alpha asymmetries compared to controls (Bartolomeo et al., 2019). However, in the above-mentioned study LFA was inversely correlated with the severity of negative symptoms. The absence of this correlation in our study may be related to the different sample of participants that we tested. Indeed, differently from individuals at clinical high risk for psychosis, healthy subjects with high PS symptoms have a reduced distress/and or help-seeking behaviour (van Os et al., 2009).

Lastly, some limitations of the current study should be addressed. First, as we mentioned earlier, despite the usefulness of our effort-based decision task in controlling for temporal confounds, we did not find that participants discounted rewards across schedules (as it has been shown in studies using similar paradigms) (Chong et al., 2016; Bonelle et al., 2015). Further studies should carefully control for this aspect, using rewards that would avoid the paradoxical effect of increasing action vigour in

paradigms in which motivation is operationalized as the exerted effort (Oudiette et al., 2019). Second, although the two groups of participants were matched for gender, overall our sample included mainly females. Therefore, we could not take into account gender differences in the expression of subclinical psychotic symptoms (Barajas et al.. 2015). Third, further analysis of our EEG data are needed. Particularly, asymmetry scores should be computed also by clustering EEG electrodes into regions of interest (see Fuggetta et al., 2014). Moreover, it would be interesting to compute asymmetry scores from other EEG frequency bands since motivational processes have been related also to other EEG oscillations (e.g., delta frequency band) (see Knyazev, 2012 for a review). Lastly, resting EEG may not be as powerful to detect individual differences in motivated behavior as task-activated EEG and fMRI paradigms since it allows to measure tonic cortical processes but not how these processes change during reward valuation (Coan et al., 2006; Peterson et al., 2008).

In conclusion, this was the first study to examine alpha asymmetry as a biomarker of temporal and effort cost decision making impairments in individuals with subclinical psychotic symptoms. Our result are (at least in part) in line with studies on schizophrenia and with our previous study on individuals with subclinical psychotic symptoms by showing that aberrant temporal and effort discounting of rewards can be altered prior to the onset of psychotic illness. The current findings provide an important extension to the neural mechanisms underlying motivation impairments in these subjects. Further studies on individuals with subclinical psychotic symptoms but with higher levels of negative symptoms are needed.

CHAPTER 4 - GENERAL DISCUSSION

Motivation is a complex and fundamental component of human behavior, necessary to obtain basic needs and pursuing goals. The past decade has seen a flourishing of studies investigating neural and behavioral correlates of motivation in healthy individuals as well as the mechanisms underlying disorders in which abnormal motivation plays a major role. Much of the work discussed in this thesis involved two processes that have been considered as likely contributors of abnormal motivation across neurological and psychiatric disorders: reward responsiveness (reward liking and wanting) and reward valuation (effort and temporal discounting of reward). Studies providing evidences for impairments in these constructs may be critical to understanding facets of motivational behaviors and also to reduce negative health outcome of patients with disorders of motivation (Zald et al., 2017; Epstein et al., 2015; Voon et al., 2017)

Therefore, the experimental work included in this thesis aimed at extending the knowledge on impairments of reward responsiveness and reward valuation in disorders of motivation, with a specific focus on those of excessive and diminished motivation (Voon et al., 2017; Napier et al., 2015; Husain et al., 2018). With this goal, I have conducted four studies on different clinical populations, as well as on individuals at clinical high risk, by using a wide variety of research methods including behavioral paradigms, psychophysiological measures (heart rate, skin conductance), tDCS and EEG in order to investigate the neural and behavioral correlates of their disorders of motivation.

More in details, in Chapter 2 I have discussed two studies (Study 1 and Study 2) on PD patients with ICD (as an example of excessive motivation), whereas in Chapter 3 two studies (Study 3 and Study 4) on healthy individuals with risk of psychosis experiencing negative symptoms (as an example of diminished motivation) were discussed.

As regards the rationale of Study 1, the starting point was represented by studies showing an increased activity in different reward brain regions such as the ventral striatum after reward presentation in PD patients with ICDs compared to control patients (O'Sullivan et al., 2011; Evans et al., 2006; Steeves

et al., 2009; Politis et al., 2013), and that 'wanting' but not 'liking' ratings in these patients significantly correlate with the activity in the ventral striatum (Evans et al., 2006; Steeves et al., 2009). These findings have suggested that, in line with the incentive sensitization theory (Robinson and Barridge, 1992; Berridge and Robinson, 2016), ICD may arise from excessive attribution of wanting (or incentive salience) to rewards. However, the hypothesis of this enhanced reward responsiveness had never been tested in a specific type of ICD in PD such as binge eating (BE). Therefore, to fill this gap, we tested this hypothesis by asking PD patients with and without BE and healthy controls to perform different explicit and implicit experimental tasks assessing food liking and wanting. Our results showed that PD patients with BE display an altered liking for sweet foods but not increased wanting. Importantly, this difference emerged only when implicit measures were used, while no differences emerged in self-report ratings of liking and wanting. These findings suggest that BE in PD patients is preferably associated with altered implicit liking for rewards or, more in general, with affective abnormalities.

Based on the results of Study 1, as well as on studies showing that not only reward responsiveness but also reward valuation processes might be potential responsible of the phenomenology of ICD in PD (Voon et al., 2011; 2017; Santangelo et al., 2017), we performed another study (Study 2) aimed at testing whether alterations in reward responsiveness and reward valuation were present in PD patients with different ICD. Moreover, we explored through tDCS the role of the left DLPFC in these alterations. Our results showed a greater reward responsiveness (for both liking and wanting) and a steeper temporal discounting of rewards in PD+ICD patients (Politis et al., 2013; O'Sullivan et al., 2011; Voon et al., 2010; Housden et al., 2010). In addition, results showed that tDCS may be capable to modulate the altered intensity of PD+ICD patients' liking, but not their altered wanting and temporal discounting of rewards. This effect might be explained by the enhanced cognitive control exerted by the DLPFC over the vmPFC, which might be involved in the abnormal affective/hedonic responses to appealing stimuli in PD+ICD.

Taken together, results of Study 1 and Study 2 confirm previous studies showing altered wanting in PD patients with ICD. In addition, both studies suggest that ICD in PD are associated not only with altered wanting but also with altered liking, or, more in general, with affective abnormalities. These results are further corroborated by the correlation found in Study 1 between BE and self-reported depression. However, previous studies on affective factors have shown inconclusive findings, as an association between depression and anxiety with ICD in PD was sometimes found (Erga et al., 2017¸Clark and Dagher, 2014; Leroi et al., 2011; Martini et al., 2018) and sometimes not (Bentivoglio et al., 2013; MacK et al., 2013; Piray et al., 2014). Importantly, in Study 2 we showed that affective factors in PD+ICD can be mediated by the activity of the DLPFC, suggesting the role of this area in modulating affective/hedonic responses in PD+ICD.

Differently from Chapter 2, in Chapter 3 I aimed to investigate reward valuation in a second category of motivational deficits such as disorders of diminished motivation. Particularly, I was interested in studying negative symptoms, that are commonly observed in patients with schizophrenia and across the psychosis continuum (Epstein et al., 2015; Zald et al., 2017). The interest on negative symptoms in psychosis was driven from studies reporting greater temporal and effort discounting in patients with schizophrenia relative to healthy controls (Heerey et al., 2011; Yu et al., 2017; Fervaha et al., 2013; Gold et al., 2013). Importantly, those studies have also shown that the devaluation of rewards associated with delays or effort correlate with the severity of negative symptoms, in particular avolition and anhedonia (Gold et al., 2013; Ahn et al., 2011). Since contemporary models of psychosis suggest that aberrant reward valuation and reward responsiveness are involved in the cause of psychotic disorders (van Os et al., 2009), studying these alterations at earlier stages of the disease across the psychosis continuum may be useful for early detection and intervention. Therefore, we investigated in Chapter 3 whether deficits in temporal and effort cost computations could be observed also in healthy individuals with subclinical psychotic symptoms (PS) to determine if this dysfunction was already present in a potentially pre-psychotic period.

More in details, we first conducted a behavioral study (Study 3) on individuals with different levels of subclinical PS and we asked them to perform two temporal discounting tasks with food and money rewards (primary and secondary rewards, respectively) and one effort discounting task with food. Interestingly, we found that high PS show a constant subjective value as time delay increases, which means that they are not sensitive to changes in discounting rates and temporal delays, while in the effort discounting task they tended to show a reduced willingness to work to obtain rewards when the required effort is high. Importantly, participants exerting less effort in the higher effort condition were those with higher negative symptoms. Our results are (at least in part) in line with studies conducted with schizophrenia patients (Fervaha et al., 2013; Gold et al., 2012; Fusar-Poli et al., 2013), and extend current knowledge by showing that aberrant temporal and effort discounting of rewards are observed in healthy individuals with subclinical psychotic symptoms and therefore might be a vulnerability marker for psychosis.

Based on the results of Study 3, we aimed to replicate our findings in a second study (Study 4), and to explore whether resting left frontal alpha asymmetry (LFA), used as an electrophysiological index of motivation and impulsivity, could be a biomarker of altered motivation in these subjects.

Results were (at least in part) in line with studies on schizophrenia and with Study 3 by showing that aberrant temporal and effort discounting of rewards can be altered prior to the onset of psychotic illness. Importantly, LFA was found to be significantly associated with the willingness to exert effort in the hardest schedule of the effort-based task for high PS individuals but not for those with low PS. Taken together, result of Study 3 and Study 4 suggest that aberrant temporal and effort cost computations might be present in individuals with subclinical PS. Moreover, the LFA results of Study 4 suggest also an higher sensitivity to the cost of effort in these subjects, providing a possible electrophysiological correlate of their altered reward valuation.

More in general, some considerations are needed with respect to the results that emerged from the studies presented in this thesis. As mentioned earlier, we found in Chapter 2 that disorders of excessive motivations such as ICD in PD are characterized by alterations not only in the wanting

component of reward responsiveness but also in its liking one. Therefore, our findings are only partially in line with the incentive sensitization theory, which posits that wanting for rewards may grow over time independently of reward liking as an individual develops ICD in PD (Napier et al., 2015). One possible explanation for this altered liking or affective reactions to rewards may be linked to the presence of affective disorders, which commonly accompany ICD in PD (Aminian and Strafella, 2013). Therefore, the altered liking of PD+ICD patients is more in line with other theories of addiction as, for instance, the reward deficiency theory (RDS) (Bloom et al., 2000). According to this theory, addictive behaviors are characterized by a hypoactivation of brain reward pathways mediating pleasurable experience from rewards. Consequently, this altered consummatory pleasure of PD+ICD patients might emerge in order to compensate this deficiency and stimulate brain reward areas. It is thus possible that ICD in PD may usurp neural circuitry involved in not only incentive motivation but also pleasure. Interestingly, we found that affective factors in PD+ICD can be mediated by the activity of the DLPFC, suggesting the role of this area in modulating their affective/hedonic responses. We propose that the DLPFC may have a role in cognitive control over affective/hedonic responses to appealing stimuli in PD+ICD, and that this role could be mediated by the activity of the DLPFC over the ventromedial prefrontal cortex (vmPFC), which has been associated to the consummatory process of reward (Hare et al., 2009).

As to reward valuation processes, in Study 2 I found that PD+ICD patients showed greater TD of rewards compared to controls. It is possible that their greater TD might be derived from an excessive incentive salience to rewards, as a result of the above mentioned altered dopaminergic transmission in the ventral striatum (Housden et al., 2010). It has been proposed that aberrant incentive salience not only does it lead to a pathological pursuit of rewards but also to irrational choices in order to get rewards, as in the intertemporal choices tasks (Robinson and Berridge, 1993; Voon et al., 2010, 2017). Another complementary explanation is that high levels of impulsivity of PD+ICD patients might be mediated from excessive dopaminergic transmission in frontal regions, which in turn alter their reward valuation processes (Housden et al., 2010; Cools, 2006). Therefore,

fronto-striatal projections may be especially important in regulating emotions and providing inhibitory control during reward responsiveness and reward valuation processes in PD+ICD patients (Voon et al., 2017).

As to the other end of the behavioral DA-dependent continuum (see Chapter 1), the aberrant salience model of psychosis (Kapur et al., 2005) posits that anhedonia and other predominantly affective negative symptoms in schizophrenia (as an instance of diminished motivation) might be related to a dysfunction of dopaminergic neurons in the ventral striatum (Juckel et al., 2006; Goldstein and Volkow, 2002). This model proposed that a high striatal dopamine turnover may increase the "noise" in the reward system, thus interfering with the neuronal processing of reward-predicting cues by phasic dopamine release. This, in turn, might contribute to negative symptoms such as anhedonia (Juckel et al., 2006). According to another model of psychosis, such as the cognitive control model (Lesh et al., 2011; Papanastasiou et al. 2018), psychotic symptoms arise as a consequence of decreased cognitive control. Therefore, hypofrontality and functional disconnectivity of fronto-striatal circuits may represent a marker for psychosis (Modinos et al., 2010; Papanastasiou et al., 2018). Interestingly, as regards individuals with risk for psychosis, a combination of the aberrant salience and cognitive control hypotheses has been proposed (Papanastasiou et al., 2018; van Os and Kapur, 2009). More in details, this model suggests that the attribution of significance to irrelevant perceptual stimuli presence (aberrant salience) might generate psychotic-like experiences. However, these experiences may become clinically relevant symptoms only if they affect cognitive control mechanisms. Importantly, results of Studies 3-4 showed that aberrant reward valuation processes, such as altered effort and temporal discounting of rewards, might be present not only in patients with schizophrenia but also in healthy individuals with high PS. In addition, findings of Study 4 suggest an enhanced neural sensitivity in frontal areas (LFA derived from frontal F4-F3 electrodes) to the cost of effort during the decision making processes about rewards in individuals with high PS. Interestingly, it has been proposed that an increased frontal activity during reward anticipation in individuals at ultra-high risk for psychosis (Juckel et al., 2012), as well as in healthy individuals with

high PS, serves as a compensatory frontal executive process which prevent the evolution of clinically relevant psychotic symptoms (Papanastasiou et al., 2018). Therefore, the results of Study 4 are also in line with a model which combines aberrant salience and cognitive control to understand the mechanisms underlying psychotic-like experiences.

Another import consideration with respect to the studies discussed in this thesis is the use of primary rewards in examining reward responsiveness and reward valuation processes. Particularly, only a few studies have used primary reinforces such as food in investigating disorders of motivation in individuals with PD (Girard et al., 2019) and individuals within the psychosis continuum (Waltz et al., 2009; Grimm et al., 2012). However, using foods as reinforces offers the opportunity first, to investigate separately anticipatory and consummatory pleasure and, secondly, to draw closer comparisons with findings in animal research, whereby a considerable amount of studies on rewards have employed primary reinforces such as food and liquid (Berridge et al., 2010). Moreover, foods are also the most accessible experimental stimuli available to neuroscience studies of pleasure (Kringelbach and Berridge 2010). Several studies have found that the anticipatory pleasure for high-calorie food leads to the activation of the mesocorticolimbic reward system (O'Doherty et al., 2002; Simon et al., 2014) while food consummatory pleasure mainly involves the primary (insula/frontal operculum), as well as the secondary gustatory cortex (lateral OFC) (O'Doherty et al., 2002; Rolls, 2007). Interestingly, a similar pattern of activation has been found during the processing of abstract visual food stimuli (Beaver et al., 2006; Simon et al., 2015).

Thus, the food rewards in the effort discounting tasks of Study 3 and Study 4 allowed us to selectively measure how participants were willing to work for high-calorie snacks compared to low-calorie foods, when both foods were equally liked. Moreover, in the temporal discounting task (see Study 3), in which both food and money rewards were employed, participants with high PS' rate of discounting appeared linear and flatter than that exhibited by participants with medium and low PS. Importantly, this result was particularly evident when we used food rewards.

Therefore, my results suggest that, since primary rewards such as food are innately and immediately rewarding (see Chapter 1) and allow better disentangling reward liking and reward wanting, they are more appropriate to investigate disorders of excessive and diminished motivation than secondary rewards such as money, whereby the stimulus value is abstractly linked to future reward attainment. In the light of these considerations, I suggest that future studies, possibly combining behavioral and neuroimaging measures, would help to elucidate the neurobiological mechanisms underpinning the results that emerged from this thesis. Specifically, as to reward responsiveness in disorders of motivation, it would be of great interest to utilize tasks that can better dissociate neural responses associated with liking and wanting of rewards. One possible candidate might well be a "food incentive delay" (FID) task (Simon et al., 2015) performed by participants in an MR scanner. This task is a modified version of the MID (Knutson et al., 2001), in which participants learn to respond to a cue (conditioned stimulus), for example, by pushing a button. If the response they provide is appropriate, then they receive a reward. This task allows us to separately investigate both anticipatory (the expectation of a reward after cue presentation) and consummatory (the hedonic impact experienced during the receipt of reward) pleasure. In particular, in the FID participants can earn "snack points" (SP) which they then could exchange for sweet and salty snacks after the MRI. As to reward valuation processes, it would interesting to employ temporal discounting tasks that can dissociate neural responses associated with delay discounting from those associated with reward magnitude. Lastly, for what concerns the effort discounting tasks, it is important to develop paradigms that rule out temporal confounds.

To conclude, as I hope I clarified in my dissertation, motivated behavior involves several factors including reward liking and wanting (reward responsiveness) as well as temporal and effort discounting of rewards (reward valuation). These are of course simplified examples and do not reflect all possible interactions among brain systems involved in the vast complexity of motivated behavior in everyday life. However, partitioning of motivated behavior into its components can provide a framework that will deepen and enrich understanding of separate and sometimes dissociable (e.g.,

reward liking and wanting) neurobiological underpinnings of these behaviors. Moreover, studies involving clinical and subclinical populations with motivational impairments are fundamental to test the above mentioned hypothesis about common and distinct mechanisms involved in motivation. As a last point, since motivational impairments are critical to functional deficits in both neurological and psychiatric diseases, evidence from my studies could eventually lead to more specific and targeted interventions that could help quality of life and reduce public health burden.

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Appendix A
Supplementary results of Chapter 2

Study 1

Table S2.1 Patients with Parkinson's disease with binge eating

Subjects	Sex	Age	Other ICDs
S1	f	64	PG
S2	f	70	
S3	f	65	
S4	m	72	HB, PU
S5	m	63	HS
S6	f	75	CS, HB
S7	m	77	HS, HB, PU
S8	f	68	HB, PU
S9	f	77	HB, PU
S10	m	64	
S11	f	68	CS
S12	m	71	CS
S13	f	75	
S14	m	53	
S15	m	65	HB
S16	m	47	

HB = hobbyism; PU = Punding; HS = hypersexuality;
CS =compulsive shopping; PG = pathological gambling

Table S1.2 Neuropsychological data (mean and standard deviation)

	PD+BE (n=16)	PD (n=15)	C (n=20)
MMSE	28.2(1.8)	29.2(0.8)	29.1(1.6)
FAB	15.4(2.2) ≠	16.6(1.3)	19.1(1.1)
Semantic Fluency [a]	41 (9.9) ≠	43.6 (11.2)	47.2 (7.8)
TMT a	54.8 (29.6)	53.1 (36.1)	39.4 (14.8)
TMT b	163.2 (128.7)	127.8 (60.7)	108.8 (48.9)
TMT b-a [b]	108.6 (118.6)	77.3 (44.4)	69.6 (40.7)
Attentive Matrices [c]	43.1 (4.9)	45 (3.7)	46 (3)
Digit Span Forward	5.5 (1.2) *	6.3 (0.8)	6.2 (1.1)
Rey's 15-word test: immediate recall	39.4 (11.4)	40.9 (12.4)	45.8 (11.3)
Rey's 15-word test: delayed recall	8.2 (3.6)	9.4 (3.5)	9.1 (3.8)
Poppelreuter-Ghent Test [d]	63.1 (7.1)	63.3 (9.6)	65.5 (8)

* = significantly different from PD, $p < 0.05$;
≠ = significantly different from C, $p < 0.05$;
a = one patient was unable to perform the Semantic Fluency test;
b = two patients were unable to perform the Trail Making Test;
c = two patients were unable to perform the Attentive Matrices Test;
d = six patients were unable to perform the Poppelreuter-Ghent Test

Table S2.3. Dopamine agonists and dosages

Patient	Group	Dopamine agonist	Dosage
PD1	PD	Pramipexole	1.05
PD2	PD+BE	Pramipexole	1.05
PD3	PD	Pramipexole	2.1
PD4	PD+BE	Pramipexole	1.05
PD5	PD	Pramipexole	2.1
PD6	PD+BE	Pramipexole	1.05
PD7	PD	Pramipexole	1.05
PD8	PD	Pramipexole	1.05
PD9	PD+BE	Rotigotine	8
PD10	PD	Rotigotine	6
PD11	PD+BE	Rotigotine	6
PD12	PD+BE	Pramipexole	0.7
PD13	PD	Rotigotine	8
PD14	PD	Pramipexole	2.27
PD15	PD	Pramipexole	1.05
PD16	PD	Pramipexole	2.1
PD17	PD	Ropinirole	6
PD18	PD+BE	Pramipexole	1.05
PD19	PD	Pramipexole	2.1
PD20	PD+BE	Pramipexole	2.1
PD21	PD	Pramipexole	2.1
PD22	PD	Pramipexole	0.78
PD23	PD	Pramipexole	2.1
PD24	PD+BE	Ropinirole	8
PD25	PD+BE	Rotigotine	8
PD26	PD+BE	Pramipexole	1.05
PD27	PD+BE	Rotigotine	8
PD28	PD+BE	Pramipexole	1.57
PD29	PD+BE	Pramipexole	1.05
PD30	PD+BE	Rotigotine	8
PD31	PD+BE	Rotigotine	8

Dosage is expressed in milligrams (mg)

Comparison between groups

Demographic data:

PD+BE, PD and C were matched for gender (PD+BE vs PD: $\chi2(1) = 0$, $p = 1$; PD+BE vs C: $\chi2(1) = 0.10$, $p = 0.74$; PD vs C: $\chi2(1) = 0.03$, $p = .84$); age (PD+BE vs PD: $U = 119.5$, Z = -0.02, $p = 0.98$; PD+BE vs C: $U = 142.5$, Z = -0.56, $p = 0.58$; PD vs C: $U = 135$, Z = -0.50, $p = 0.62$) and education (PD+BE vs PD: $U = 99.5$, Z = -0.81, $p = 0.39$; PD+BE vs C: $U = 131$, Z = -0.92, $p = 0.36$; PD vs C: $U = 149$, Z = -0.03, $p = 0.97$). PD+BE had a significantly higher BMI compared to PD (U = 35, Z = 2.14, p = 0.03) and C (U = 57, Z = 1.99, p = 0.05).

Clinical data

The PD+BE group scored significantly higher, compared to the PD group, on the QUIP-RS sub-scale for eating ($U = 0$, Z = 4.74, $p < 0.01$), buying ($U = 35.5$, Z = 3.34, $p < 0.01$), hobbyism ($U = 47$, Z = 2.89, $p < 0.01$), and total QUIP-RS score [t (29) = 4.38, $p = < 0.01$]. Instead, they did not differ for gambling ($U = 94$, Z = 1.03, $p = 0.30$), hyper-sexuality ($U = 101.5$, Z = 0.73, $p = 0.46$), punding ($U = 79$, Z = 1.62, $p = 0.10$) and compulsive medication use ($U = 86$, Z = 1.34, $p = 0.18$) sub-scales.

Neuropsychological data and questionnaires

The three groups did not differ on HADS sub-scale for anxiety (PD+BE vs PD: [t (28) = 1.48, $p = 0.15$]; PD+BE vs C: [t (33) = 1.80, $p = 0.08$]; PD vs C: [t (33) = 0.13, $p = 0.90$]. No differences were observed regarding the BIS-11 total score (PD+BE vs PD: [t (29) = 1.05, $p = 0.30$]; PD+BE vs C: [t (34) = -0.64, $p = 0.53$]; PD vs C: [t (33) = -1.79, $p = 0.08$]) or its attentional (PD+BE vs PD: [t (29) = 1.03, $p = 0.31$]; PD+BE vs C: [t (34) = -0.54, $p = 0.59$]; PD vs C: [t (33) = -1.65, $p = 0.11$]), motor (PD+BE vs PD: [t (29) = 1.03, $p = 0.31$]; PD+BE vs C: [t (34) = -0.16, $p = 0.88$]; PD vs C: [t (33) = -1.25, $p = 0.22$]) and non-planning (PD+BE vs PD: $U = 107$, Z = -0.51, $p = 0.61$; PD+BE vs C: $U = 131.5$, Z = -0.91, $p = 0.36$; PD vs C: $U = 146.5$, Z = -0.12, $p = 0.91$) sub-scales. No difference emerged in the BAS total score (PD+BE vs PD: [t (29) = -0.31, $p = 0.76$]; PD+BE vs C:

[t (34) = -0.98, p = 0.33]; PD vs C: [t (33) = -0.46, p = 0.65]) and on BAS reward responsiveness (PD+BE vs PD: U = 101, Z = 0.75, p = 0.44; PD+BE vs C: U = 160, Z = 0, p = 1; PD vs C: U = 128, Z = -0.73, p = 0.46) and BAS drive (PD+BE vs PD: U = 120, Z = 0, p = 1; PD+BE vs C: U = 151.5, Z = 0.27, p = 0.79; PD vs C: U = 141, Z = 0.30, p = 0.76) subscales. However, the PD+BE group scored lower, compared to C on the BAS fun-seeking sub-scale (U = 99.5, Z = -1.93, p = 0.05). No differences were found between the PD+BE and PD participants (U = 116.5, Z = -0.14, p = 0.89), and between PD and C participants (U = 116.5, Z = -1.12, p = 0.26) on this sub-scale. See **Table 2.1**.

Participants did not significantly differ on MMSE scores (PD+BE vs PD: U = 76, Z = -1.74, p = 0.08; PD+BE vs C: U = 104.5, Z = -1.77, p = 0.08; PD vs C: U = 149, Z = 0.03, p = 0.97). PD+BE scored lower compared to C on the FAB (U = 89, Z = -2.26, p = 0.02), while no difference was observed between PD+BE and PD (U = 81.5, Z = -1.52, p = 0.13), and between PD and C (U = 130.5, Z = -0.65, p = 0.52). Also, PD+BE group scored lower compared to C on Semantic Fluency test [t (33) = -2.07, p = 0.05], while no difference was observed on this test between PD+BE and PD [t (28) = -0.66, p = 0.52] and between PD and C participants [t (33) = -1.14, p = 0.26]. Furthermore, participants did not significantly differ on TMT B-A (PD+BE vs PD: U = 100.5, Z = 0.20, p = 0.84; PD+BE vs C: U = 111.5, Z = 0.78, p = 0.43; PD vs C: U = 124, Z = 0.64, p = 0.52); Attentive Matrices test (PD+BE vs PD: U = 94.5, Z = -1.00, p = 0.31; PD+BE vs C: U = 95.5, Z = -1.67, p = 0.09; PD vs C: U = 116, Z = -0.69, p = 0.49), on Rey's 15-word test (immediate recall) (PD+BE vs PD: [t (29) = -0.35, p = 0.73]; PD+BE vs C: [t (34) = -1.67, p = 0.10]; PD vs C: [t (33) = -1.20, p = 0.24]), on Rey's test (delayed recall) (PD+BE vs PD: [t (29) = -0.89, p = 0.38]; PD+BE vs C: [t (34) = -0.67, p = 0.50]; PD vs C: [t (33) = 0.24, p = 0.81]), and on Poppelreuter-Ghent Test (PD+BE vs PD: U = 71.5, Z = -0.35, p = 0.72; PD+BE vs C: U = 90, Z = -1.17, p = 0.24; PD vs C: U = 115, Z = -0.55, p = 0.58). However, the PD+BE group scored lower, compared to the PD group, on Digit Span Test (U = 69, Z = -2.02, p = 0.04). No differences were found between the PD+BE and C

participants (U = 109.5, Z = -1.61, p = 0.11), and between PD and C participants (U = 132, Z = 0.60, p = 0.55).

Study 2

Stimuli

Reward and non-reward pictures (excluding dopamine replacement therapies pictures) were selected through a questionnaire filled out by an independent sample of participants (n = 53) and were matched for brightness ($F_{1, 18}$ = 1.51, p = 0.23), visual complexity ($F_{1, 18}$ = 3.05, p = 1.00), arousal ($F_{1, 18}$ = 0.05, p = 0.82), valence ($F_{1, 18}$ = 0.45, p = 0.51) and familiarity ($F_{1, 18}$ = 0.11, p = 0.74).

Comparison between groups

Demographic data

PD+ICD, PD and C were matched for gender [χ^2 (2) = 0.63, p = 0.73], age ($F_{2, 40}$ = 0.44, p = 0.65), education [χ^2 (2) = 1.22, p = 0.54], and BMI ($F_{2, 40}$ = 0.60, p = 0.55). In addition, they did not significantly differ on subjective ratings of hunger [PD+ICD: χ^2 (2) = 0.16, p = 0.92; PD: χ^2 (2) = 2.72, p = 0.26; C: χ^2 (2) = 0.30, p = 0.86] and fasting [PD+ICD: χ^2 (2) = 1.59, p = 0.45; PD: χ^2 (2) = 0.83, p = 0.66; C: χ^2 (2) = 0.38, p = 0.83] across the three experimental sessions.

Clinical and questionnaire data

The Kruskal-Wallis ANOVA on QUIP-RS sub-scale for **eating** showed a main effect of group [χ^2 (2) = 26.34, p < 0.001]. The Mann–Whitney U test showed that PD+ICD scored higher on this sub-scale compared to PD (U = 22.50, Z = -3.51, p < 0.001) and C (U = 8.00, Z = 4.45, p < 0.001). A

higher score on this sub-scale was observed also for PD compared to C (U = 35.00, Z = 3.03, p < 0.01).

The Kruskal-Wallis ANOVA on QUIP-RS sub-scale for **hyper-sexuality** showed a main effect of group [χ^2 (2) = 6.38, p = 0.04]. The Mann–Whitney U test showed that PD+ICD tendentially scored higher on this sub-scale compared to PD (U = 60.00, Z = -1.89, p = 0.06). Moreover, PD+ICD scored significantly higher on this sub-scale compared to C (U = 63.50, Z = 2.26, p = 0.02), while no statistically significant differences emerged between PD and C (U = 91.50, Z = 0.34, p = 0.73).

The Kruskal-Wallis ANOVA on QUIP-RS sub-scale for **gambling** did not show a main effect of group [χ^2 (2) = 0, p = 1].

The Kruskal-Wallis ANOVA on QUIP-RS sub-scale for **buying** did not show a main effect of group [χ^2 (2) = 1.36, p = 0.51].

The Kruskal-Wallis ANOVA on QUIP-RS sub-scale for **hobbysm** showed a main effect of group [χ^2 (2) = 15.71, p < 0.001]. The Mann–Whitney U test showed that PD+ICD scored higher on this sub-scale compared to PD (U = 39.50, Z = -2.73, p < 0.01) and C (U = 30.50, Z = 3.60, p < 0.001), while no statistically significant differences emerged between PD and C (U = 64.50, Z = 1.74, p = 0.08).

The Kruskal-Wallis ANOVA on QUIP-RS sub-scale for **punding** showed a main effect of group [χ^2 (2) = 8.42, p = 0.01]. The Mann–Whitney U test showed that PD+ICD scored higher on this sub-scale compared to PD (U = 58.50, Z = -2.50, p = 0.01) and C (U = 63.50, Z = 2.26, p = 0.02), while no significant differences emerged between PD and C (U = 84.50, Z = -1.34, p = 0.18).

The Kruskal-Wallis ANOVA on QUIP-RS sub-scale for **compulsive medication use** showed a main effect of group [χ^2 (1) = 4.98, p = 0.03]. The Mann–Whitney U test showed that PD+ICD scored higher on this sub-scale compared to PD (U = 48.00, Z = -2.23, p = 0.03).

The Kruskal-Wallis ANOVA on QUIP subscale for ICDs (**eating, hyper-sexuality, gambling and buying** pooled together) showed a main effect of group [χ^2 (2) = 23.04, p < 0.001]. The Mann–Whitney U test showed that PD+ICD scored higher on this sub-scale compared to PD (U = 23.50, Z

= -3.48, $p < 0.001$) and C ($U = 12.50$, Z = 4.17, $p < 0.001$). A higher score on this sub-scale was observed also for PD compared to C ($U = 47.50$, Z = 2.34, $p = 0.02$).

The one-way ANOVA on QUIP-RS **total score** showed a main effect of group ($F_{2, 40} = 35.87$, $p < 0.001$). Post-hoc analysis showed that PD+ICD scored higher on QUIP-RS total score compared to PD ($p < 0.001$) and C ($p < 0.001$), while no significant differences emerged between PD and C ($p = 0.32$).

The one-way ANOVA on **HADS anxiety sub-scale** showed a main effect of group ($F_{2, 38} = 5.33$, $p < 0.01$). Post-hoc analysis showed that PD+ICD scored higher compared to C ($p < 0.01$), while no significant differences emerged between PD+ICD and PD ($p = 0.12$) and between PD and C ($p = 0.11$). The one-way ANOVA on **HADS depression sub-scale** did not show a significant result ($F_{2, 38} = 1.80$, $p = 0.18$).

Reward sensitivity task

A repeated-measure ANCOVA (controlling for age) on *liking ratings* with Group (PD+ICD, PD, C) as a between-subjects variable and Session (Sham, DLPFC, M1) and Stimuli (rewards, non-rewards) as within-subjects variable yielded a significant interaction Group x Session ($F_{2, 78} = 2.59$, $p = 0.04$). Post-hoc analysis showed that in the Sham session PD+ICD liked more the stimuli compared to PD ($p = 0.04$), while no differences emerged between C and PD+ICD ($p = 0.72$) and between C and PD ($p = 0.09$). Moreover, no differences between groups emerged in the DLPFC session (all *ps* > 0.23). Differently, in the M1 session PD+ICD and C liked more the stimuli compared to PD (PD+ICD vs PD: $p < 0.01$; C vs PD: $p = 0.04$), while no differences emerged between PD+ICD and C ($p = 0.22$). No main effects of Group ($F_{2, 39} = 2.92$, $p = 0.07$), type of Session ($F_{2, 78} = 0.54$, $p = 0.59$) and type of Stimuli ($F_{1, 39} = 0.02$, $p = 0.90$) emerged. Moreover, there were no significant Group x Stimuli ($F_{2, 39} = 2.58$, $p = 0.09$), Stimuli x Session ($F_{2, 78} = 1.63$, $p = 0.20$) and Group x Stimuli x Session ($F_{4, 78} = 0.43$, $p = 0.79$) interactions.

A repeated-measure ANCOVA (controlling for age) on *wanting ratings* with Group (PD+ICD, PD, C) as a between-subjects variable and Session (Sham, DLPFC, M1) and Stimuli (rewards, non-rewards) as within-subjects variables yielded a significant main effect of Group ($F_{2, 39} = 3.99$, $p = 0.03$) and a marginally significant interaction Group x Stimuli ($F_{2, 39} = 3.08$, $p = 0.057$). There was no main effect of Session ($F_{2, 78} = 1.34$, $p = 0.44$), as well as of Stimuli ($F_{1, 39} = 0.27$, $p = 0.61$). No significant Group x Session ($F_{2, 78} = 1.91$, $p = 0.12$), Session x Stimuli ($F_{2, 78} = 1.99$, $p = 0.14$) and Group x Session x Stimuli ($F_{4, 78} = 0.77$, $p = 0.55$) emerged.

Post-hoc analysis on the main effect of group showed a higher wanting for PD+ICD participants compared to PD participants ($p = 0.01$) and C participants ($p = 0.04$), while no differences emerged between PD and C participants ($p = 0.54$). As regards the marginally significant interaction Group x Stimuli, PD+ICD wanted more rewards compared to PD ($p = 0.046$) and C ($p = 0.01$), while no differences emerged between PD and C ($p = 0.63$). Moreover, PD+ICD wanted also more non-reward compared to PD ($p < 0.01$), while no differences emerged between PD+ICD and C ($p = 0.23$) and between PD and C ($p = 0.11$).

A repeated-measure ANCOVA (controlling for age) on *HR values* during the presentation of the stimuli with Group (PD+ICD, PD, C) as a between-subjects variable and Session (Sham, DLPFC, M1) and Stimuli (rewards, non-rewards) as within-subjects variables yielded no main effects of Group ($F_{2, 36} = 0.34$, $p = 0.71$), type of Session ($F_{2, 72} = 0.25$, $p = 0.77$) and type of Stimuli ($F_{1, 36} = 0.07$, $p = 0.79$). No significant Group x Session ($F_{4, 72} = 0.77$, $p = 0.55$), Group x Stimuli ($F_{2, 36} = 1.06$, $p = 0.36$), Session x Stimuli ($F_{2, 72} = 1.90$, $p = 0.16$) and Group x Session x Stimuli ($F_{4, 72} = 0.76$, $p = 0.55$) interactions emerged.

A repeated-measure ANCOVA (controlling for age) on *SCR magnitude values* during the presentation of the stimuli with Group (PD+ICD, PD, C) as a between-subjects variable and Session (Sham, DLPFC, M1) and Stimuli (rewards, non-rewards) as within-subjects variables yielded no main effects of Group ($F_{2, 36} = 1.67$, $p = 0.20$), type of Session ($F_{2, 72} = 2.20$, $p = 0.12$) and type of Stimuli ($F_{1, 36} = 0.00$, $p = 0.97$). No significant Group x Session ($F_{4, 72} = 0.75$, $p = 0.56$), Group x

Stimuli ($F_{2, 36} = 0.33$, $p = 0.72$), Session x Stimuli ($F_{2, 72} = 2.64$, $p = 0.08$) and Group x Session x Stimuli ($F_{4, 72} = 0.68$, $p = 0.60$) interactions emerged.

Temporal discounting task

A repeated-measure ANCOVA (controlling for age) on AUC values with Session (Sham, DLPFC, M1) and type of Task (money, food) as within-subjects variables and Group (PD+ICD, PD, C) as a between-subjects variable yielded no main effect of Group ($F_{2, 38} = 2.49$, $p = 0.10$) nor of type of Session ($F_{2, 76} = 0.03$, $p = 0.97$) and no main effect of Task ($F_{1, 38} = 1.83$, $p = 0.18$). No interactions Group x Session ($F_{4, 76} = 1.41$, $p = 0.24$), Task x Group ($F_{2, 38} = 0.11$, $p = 0.90$), Task x Session ($F_{2, 76} = 0.86$, $p = 0.43$) and Task x Session x Group ($F_{4, 76} = 0.22$, $p = 0.93$) emerged.

A repeated measure ANCOVA (controlling for age) on hyperbolic log-transformed *K* with Session (Sham, DLPFC, M1) and type of Task (money, food) as within-subjects variables and Group (PD+ICD, PD, C) as a between-subjects variable values showed a main effect of Group ($F_{2, 38} = 4.02$, $p = 0.02$), while there were not main effects of Task ($F_{1, 38} = 2.55$, $p = 0.12$) or Session ($F_{2, 76} = 0.03$, $p = 0.97$). Post hoc analysis on the main effect of Group showed that the discounting rate of PD+ICD participants was steeper compared to that of PD ($p = 0.02$) and C ($p = 0.02$) participants, while discounting rates of PD and C participants were not statistically different ($p = 0.84$). There were no significant Session x Group ($F_{4, 76} = 1.23$, $p = 0.30$), Task x Group ($F_{2, 38} = 0.34$, $p = 0.89$), Session x Task ($F_{2, 76} = 0.34$, $p = 0.63$) and Session x Task x Group interactions ($F_{4, 76} = 0.48$, $p = 0.63$).

Correlations

Table S2.4. Correlations between QUIP-Total scores and experimental tasks measures (across all PD patients) across stimuli and experimental sessions.

	QUIP total score

	Sham	*DLPFC*	*M1*
Reward sensitivity task			
Liking rewards	**0.42***	0.30	0.34
Liking non-rewards	**0.39***	0.14	0.29
Wanting rewards	**0.54****	**0.41***	**0.49****
Wanting non-rewards	**0.42***	0.22	**0.38***
HR values rewards	0.21	-0.14	-0.12
HR values non-rewards	0.38	-0.24	0.01
SCR magnitude rewards	-0.20	0.01	-0.07
SCR magnitude non-rewards	-0.16	-0.01	-0.17
TD task			
AUC food	-0.27	**-0.48***	-0.35
AUC money	-0.06	-0.10	0.01
K hyperbolic food	0.29	**0.42***	**0.44***
K hyperbolic money	0.12	0.16	-0.00

* = $p < 0.05$; ** = $p < 0.01$

Appendix B
Supplementary results of Chapter 3

Study 3

Comparison between groups

Individuals with high PS, medium PS and low PS were matched for gender [χ^2 (2) = 5.3, $p = 0.07$], age ($F_{2, 57} = 0.24$, $p = 0.78$), education ($F_{2, 57} = 0.33$, $p = 0.72$), and BMI ($F_{2, 57} = 1.23$, $p = 0.29$). In addition, they did not significantly differ on subjective ratings of hunger ($F_{2, 57} = 1.11$, $p = 0.34$).

CAPE scores

The one-way ANOVA on **frequency of positive symptoms** showed a main effect of group ($F_{2, 57}$ = 57.77, $p < 0.0001$). Post-hoc analysis showed that both individuals with high PS and medium PS scored higher on this sub-scale compared to those with low PS. In addition, individuals with high PS scored higher compared to those with medium PS (all *ps* < 0.0001).

The ANOVA on **distress of positive symptoms** showed a main effect of group ($F_{2, 57}$ = 52.08, $p < 0.0001$). Post-hoc analysis showed that both individuals with high PS and medium PS scored higher on this sub-scale compared to those with low PS. In addition, individuals with high PS scored higher compared to those with medium PS (all *ps* < 0.001).

The ANOVA on **total positive symptoms** yielded a main effect of group ($F_{2, 57}$ = 78.25, $p < 0.0001$). Post-hoc analysis showed that both participants with high PS and medium PS scored higher on this sub-scale compared to those with low PS. In addition, participants with high PS scored higher compared to those with medium PS (all *ps* < 0.0001).

The ANOVA on **frequency of negative symptoms** showed a main effect of group ($F_{2, 57}$ = 2.57, $p < 0.0001$). Post-hoc analysis showed that both individuals with high PS and medium PS scored higher on this sub-scale compared to those with low PS (all *ps* < 0.01). Furthermore, participants with high PS scored higher compared to those with medium PS ($p = 0.04$).

The ANOVA on **distress of negative symptoms** showed a main effect of group ($F_{2, 57}$ = 13.24, $p < 0.0001$). Post-hoc analysis showed that both individuals with high PS and medium PS scored higher on this sub-scale compared to those with low PS (all *ps* < 0.01). Furthermore, participants with high PS scored higher compared to those medium PS ($p = 0.05$).

The ANOVA on **total negative symptoms** scores showed a main effect of group ($F_{2, 57}$ = 13.53, $p < 0.0001$). Post-hoc analysis showed that both individuals with high PS and medium PS scored higher on this sub-scale compared to those with low PS (all *ps* < 0.01). Moreover, high PS scored higher compared to medium PS ($p = 0.04$).

The ANOVA on **frequency of depressive symptoms** showed a main effect of group ($F_{2, 57} = 8.49$, $p < 0.001$). Post-hoc analysis showed that both individuals with high PS and medium PS scored higher on this sub-scale compared to those low PS ($p < 0.001$ and $p = 0.02$, respectively). However, no statistical differences emerged between individuals with high PS and medium PS ($p = 0.07$).

The ANOVA on **distress of depressive symptoms** showed a main effect of group ($F_{2, 57} = 12.35$, $p < 0.0001$). Post-hoc analysis showed that both individuals with high PS and medium PS scored higher on this sub-scale compared to those low PS (all *ps* < 0.001). However, no statistical differences emerged between individuals with high PS and medium PS ($p = 0.1$).

The ANOVA on **total depressive symptoms** showed a main effect of group ($F_{2, 57} = 12.89$, $p < 0.0001$). Post-hoc analysis showed that both individuals with high PS and medium PS scored higher on this sub-scale compared to those low PS (all *ps* < 0.001). However, no statistical differences emerged between individuals with high PS and medium PS ($p = 0.07$).

Other questionnaires and tests

There was no main effect of Group on BDI-II scores ($F_{2, 57} = 2.53$, $p = 0.09$) nor on BIS-11 total scores ($F_{2, 57} = 1.84$, $p = 0.17$) and on BIS-11 attentional ($F_{2, 57} = 1.89$, $p = 0.16$), motor ($F_{2, 57} = 2.37$, $p = 0.10$) and non-planning ($F_{2, 57} = 0.59$, $p = 0.56$) sub-scales. In addition, there was no main effect of Group on TEPS anticipatory ($F_{2, 57} = 0.44$, $p = 0.65$) and consummatory ($F_{2, 57} = 1.57$, $p = 0.22$) sub-scales. Furthermore, there was no main effect of Group on Digit Span forward test ($F_{2, 57} = 0.28$, $p = 0.76$) and on Stroop Test for both performance time ($F_{2, 57} = 0.32$, $p = 0.73$) and number of errors ($F_{2, 57} = 0.17$, $p = 0.84$).

Concurrent Schedule Task

Participants did not differ on number of key presses for the snack option in the following Schedules: **FR2** (high PS vs low PS: $U = 166.5$, $Z = -0.41$, $p = 0.68$; high PS vs medium PS: $U = 188.5$, $Z = 0.3$, $p = 0.77$; medium PS vs low PS: $U = 182$, $Z = 0.5$, $p = 0.62$), **FR4** (high PS vs low PS: $U = 165$, $Z =$

0.45, p = 0.65; high PS vs medium PS: U = 198.5, Z = 0.02, p = 0.98; medium PS vs low PS: U = 186, Z = -0.36, p = 0.71), **FR8** (high PS vs low PS: U = 166.5, Z = -0.41, p = 0.68; high PS vs medium PS: U = 175, Z = -0.66, p = 0.51; medium PS vs low PS: U = 194, Z = -0.15, p = 0.88) and **FR16** (high PS vs low PS: U = 157, Z = -0.69, p = 0.49; high PS vs medium PS: U = 149, Z = -1.37, p = 0.17; medium PS vs low PS: U = 179.5, Z = -0.54, p = 0.59). However, in the **FR32** schedule the number of key presses was lower for individuals with high PS group compared to those with low PS (U = 114, Z = -1.94, p = 0.052). There were no differences in this schedule between individuals with high PS and medium PS, only a marginal trend (U = 132.5, Z = -1.81, p = 0.07) and between individuals with medium PS and low PS (U = 196, Z = 0.09, p = 0.92). Furthermore, there were no differences on Slope values between the three groups (only a marginal difference for individuals with high PS vs medium PS: U = 130, Z = -1.88, p = 0.06; high PS vs low PS: U = 127, Z = -1.56, p = 0.12; medium PS vs low PS: U = 196, Z = 0.09, p = 0.92).

Temporal discounting task

The ANOVA on log-transformed *k* values with Group (high PS, medium PS, low PS) x Task (food, money) yielded a significant main effect of Task ($F_{1, 57}$ = 15.48, p < 0.001), meaning a steeper temporal discounting for food than money. No other significant results emerged (*Ps* > 0.3).

Correlational analyses

Table 1B. Correlation Analyses

	Positive symptoms	**Negative symptoms**	**Depressive symptoms**
TD			
AUC food	0.03	-0.09	-0.20
AUC money	0.14	0.02	0.05
slope food	**0.38****	0.16	0.14
slope money	**0.30***	0.12	0.11
log k food	0.17	**0.30***	0.20
log k money	-0.00	0.03	0.15
Concurrent			

FR32 schedule	-0.25	**-0.27***	**-0.31***
slope	-0.21	-0.23	-0.21

* = $p < 0.05$
** = $p < 0.01$

Table 2B. Correlation Analyses between experimental tasks.

	FR32 schedule	***Slope (concurrent)***
AUC food	rho = 0.13; $p = 0.31$	rho = 0.12; $p = 0.36$
AUC money	rho = 0.10; $p = 0.44$	rho = 0.12; $p = 0.47$
Slope food	rho = -0.08; $p = 0.56$	rho = -0.06; $p = 0.66$
Slope money	rho = -0.06; $p = 0.66$	rho = -0.04; $p = 0.77$

Study 4

Comparison between groups

Individuals with high PS and low PS were matched for gender [χ^2 (1) = 0.78, $p = 0.38$], age ($F_{1, 38} = 0.08$, $p = 0.78$), education [χ^2 (1) = 1.70, $p = 0.19$], and BMI ($F_{1, 38} = 0$, $p = 0.96$). In addition, they did not significantly differ on subjective ratings of hunger ($F_{1, 38} = 1.81$, $p = 0.19$).

CAPE scores

The one-way ANOVA on **frequency of positive symptoms** showed a main effect of group ($F_{1, 38} = 93.7$, $p < 0.001$). Post-hoc analysis showed that individuals with high PS scored higher on this sub-scale compared to those with low PS ($p < 0.001$).

The ANOVA on **distress of positive symptoms** showed a main effect of group ($F_{1, 38} = 161.55$, $p < 0.001$). Post-hoc analysis showed that individuals with high PS scored higher on this sub-scale compared to those with low PS ($p < 0.001$).

The ANOVA on **total positive symptoms** yielded a main effect of group ($F_{1, 38} = 232.94$, $p < 0.001$). Post-hoc analysis showed that participants with high PS scored higher on this sub-scale compared to those with low PS ($p < 0.001$).

The ANOVA on **frequency of negative symptoms** showed a main effect of group ($F_{1, 38} = 19.88$, $p < 0.001$). Post-hoc analysis showed that participants with high PS scored higher on this sub-scale compared to those with low PS ($p < 0.001$).

The ANOVA on **distress of negative symptoms** showed a main effect of group ($F_{1, 38} = 18.68$, $p < 0.001$). Post-hoc analysis showed that participants with high PS scored higher on this sub-scale compared to those with low PS ($p < 0.001$).

The ANOVA on **total negative symptoms** scores showed a main effect of group ($F_{1, 38} = 20.44$, $p < 0.001$). Post-hoc analysis showed that participants with high PS scored higher on this sub-scale compared to those with low PS ($p < 0.001$).

The ANOVA on **frequency of depressive symptoms** showed a main effect of group ($F_{1, 38} = 21.33$, $p < 0.001$). Post-hoc analysis showed that participants with high PS scored higher on this sub-scale compared to those with low PS ($p < 0.001$).

The ANOVA on **distress of depressive symptoms** showed a main effect of group ($F_{1, 38} = 29.98$, $p < 0.001$). Post-hoc analysis showed that participants with high PS scored higher on this sub-scale compared to those with low PS ($p < 0.001$).

The ANOVA on **total depressive symptoms** showed a main effect of group ($F_{1, 38} = 28.97$, $p < 0.001$). Post-hoc analysis showed that participants with high PS scored higher on this sub-scale compared to those with low PS ($p < 0.001$).

Other questionnaires and tests

There was a main effect of Group on BDI-II scores ($F_{1, 38} = 11.67$, $p < 0.001$). Post-hoc analysis showed that participants with high PS scored higher on this sub-scale compared to those with low PS

($p < 0.01$). No main effect of Group on TEPS anticipatory ($F_{1, 38} = 1.06$, $p = 0.31$) and consummatory ($F_{1, 38} = 0.02$, $p = 0.88$) sub-scales was found. Furthermore, no main effect of Group on Digit Span forward test emerged ($F_{1, 38} = 0.61$, $p = 0.44$).

Temporal discounting task

The Kruskal-Wallis ANOVA on subjective values at 1h time delay did not show a main effect of group [χ^2 (1) = 0.26, $p = 0.61$]. No main effects of group emerged also for subjective values at 2 h [χ^2 (1) = 0.05, $p = 0.82$], 5 h [χ^2 (1) = 0.23, $p = 0.63$] and 15 h [χ^2 (1) = 0.99, $p = 0.32$] time delays.

Frequencies band power

A one-way ANCOVA (controlling for BDI) on delta frequency band power yielded no significant results ($F_{1, 35} = 1,31$ $p = 0.26$). No significant results emerged also for the following frequencies band powers: teta ($F_{1, 35} = 0.00$, $p = 0.95$); low alpha ($F_{1, 35} = 0.08$, $p = 0.78$); high alpha ($F_{1, 35} = 0.29$, $p = 0.56$), beta ($F_{1, 35} = 2.66$, $p = 0.11$).

Correlational analyses

Table 3B. Correlation Analyses between experimental tasks and CAPE

	Positive symptoms	**Negative symptoms**	**Depressive symptoms**	**TEPS antici-patory**	**TEPS Consum-matory**
TD task					
AUC food	0.00	0.07	-0.15	0.06	0.27
Slope food	0.04	-0.13	-0.03	0.07	0.23
Log k food	-0.14	-0.13	0.03	0.09	0.01
Effort task					
Medium schedule	-0.18	0.02	0.01	0.25	0.04
Hard schedule	-0.02	0.10	0.12	0.16	0.07

* = $p < 0.05$
** = $p < 0.01$

Table 3C. Correlation Analyses between experimental tasks and Alpha asymmetry scores

	Low Alpha (F4-F3)	**High Alpha (F4-F3)**	**Low Alpha (C4-C3)**	**High Alpha (C4-C3)**	**Low Alpha (P4-P3)**	**High Alpha (P4-P3)**
TD task						
AUC food	-0.06	-0.09	-0.07	-0.19	-0.07	0.08
Slope food	-0.13	-0.04	-0.03	-0.14	-0.06	0.26
Log k food	-0.11	-0.10	0.09	0.02	0.02	0.02
Effort task						
Medium schedule	0.25	0.20	0.00	-0.10	0.16	0.18
Hard schedule	0.28	0.17	-0.13	-0.27	0.35	0.10

* = $p < 0.05$
** = $p < 0.01$

Table 3D. Correlation Analyses between Asymmetry scores and CAPE

	Positive symptoms	**Negative symptoms**	**Depressive symptoms**	**TEPS antici-patory**	**TEPS Consum-matory**
Low Alpha (F4-F3)	0.11	0.04	0.00	0.18	0.06
High Alpha (F4-F3)	0.06	-0.09	-0.15	0.13	-0.03
Low Alpha (C4-C3)	-0.25	-0.18	-0.20	-0.24	-0.16
High Alpha (C4-C3)	-0.01	-0.05	-0.01	-0.32	0.11
Low Alpha (P4-P3)	-0.13	0.00	0.14	-0.09	-0.04
High Alpha (P4-P3)	0.18	-0.08	-0.03	-0.12	0.20

* = $p < 0.05$
** = $p < 0.01$

Table 3E. Correlation Analyses between experimental tasks

	Medium schedule	***Hard schedule***
AUC TD	-0.01	-0.02

Slope TD	0.27	0.29

* = $p < 0.05$
** = $p < 0.01$