Reward anticipation deficits as neuro-behavioral markers of negative symptoms in the psychosis continuum

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LES DÉFICITS D'ANTICIPATION DE LA RÉCOMPENSE COMME MARQUEURS NEURO-COMPORTEMENTAUX DES SYMPTÔMES NÉGATIFS DANS LE CONTINUUM DE LA PSYCHOSE

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Content Table

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2. Abstract

2.1 English Version

Reward anticipation is a component of motivation that has been intensely studied in the past 20 years. Using simple functional magnetic resonance imaging (fMRI) tasks like the Monetary Incentive Delay task (MID), researchers were able to assess the neural underpinnings of reward anticipation in various stages of the psychosis continuum. The psychosis continuum is a conceptual framework that hypothesizes that psychotic symptoms and experiences exist with various degrees of intensity in a spectrum ranging from health to chronic schizophrenia. The ventral striatum, in particular, has been robustly associated with reward anticipation in healthy individuals and has been brought forth as a potential marker or negative symptoms of schizophrenia. Accordingly, decreased ventral striatal activity has been shown in patients with schizophrenia, with a specific link with apathy symptoms. This deficit has not been clearly defined in other stages of the continuum, like schizotypy. Furthermore, little is known about the cortico-striatal networks at work during reward anticipation in the different stages of the psychosis continuum.

The aim of this thesis was to replicate previous activation analyses on reward anticipation, as well as to explore task-based functional connectivity in healthy participants, in individuals with high levels of schizotypy and in patients with schizophrenia. To do so, all participants performed a variant of the MID while undergoing event-related fMRI. Schizotypy was evaluated with the Schizotypy Personality Questionnaire (SPQ) and negative symptoms were assessed using the Brief Negative Symptom Scale (BNSS).

Our analyses reproduced previous findings on the neural foundations of reward anticipation in healthy individuals, showing reward responsiveness in the ventral and dorsal striatum, and cortical regions involved in motor and salience networks. We also identified the ventral striatum's link with functional networks engaged in motivation, motor, attentional, and visual processes during reward anticipation. This supports the hypothesis that the ventral striatum generates motivational salience, influencing goal-directed actions towards rewarding stimuli. In addition, we found that the processes of reward anticipation do not seem to be impacted in schizotypy. Finally, our analyses confirmed reduced ventral striatal reward responsiveness in schizophrenia and its association with apathy. However, we observed significant variability

among patient cohorts. We explored possible explanations on where that variability comes from and found that conventional evaluations of reward anticipation might not be selective enough to fully grasp the associations with negative symptoms. We further discovered that high apathy levels are associated with dysconnectivities within the salience network. These results add to previous research showing global dysconnectivity in schizophrenia.

In summary, this thesis demonstrated that reward anticipation is impacted in varying ways across the continuum of psychosis. Examining individuals at intermediate stages of the continuum, such as those classified as Ultra High Risk (UHR) or experiencing First Episode Psychosis (FEP), could contribute to determining the precise disease stage at which deficits in reward anticipation manifest.

2.2 Version Française

L'anticipation de la récompense est une composante de la motivation qui a été largement étudiée durant les 20 dernières années. En utilisant une simple tâche d'imagerie par résonance magnétique fonctionnelle (IRMf) telle que la tâche de délai de la récompense monétaire (MID), des chercheurs ont pu décrire les bases neuronales de l'anticipation de la récompense dans plusieurs niveaux du continuum de la psychose. Le continuum de la psychose est un cadre conceptuel hypothétisant que les symptômes ou expériences psychotiques existent à des niveaux degrés d'intensité sur un spectre allant de la santé à la schizophrénie chronique. Le striatum ventral en particulier a été robustement associé à l'anticipation de la récompense chez des individus sains et a été proposé comme potentiel marqueur des symptômes négatifs de la schizophrénie. En effet, une diminution de l'activité du striatum ventral a été démontrée chez les personnes souffrant de schizophrénie, avec un lien spécifique avec l'apathie. Ce déficit n'a pas été clairement défini dans d'autres niveaux du continuum, comme la personnalité schizotypique. De plus, les réseaux cortico-striataux activés par l'anticipation de la récompense sont relativement méconnus dans les différentes étapes du continuum.

Le but de cette thèse était de répliquer les précédentes analyses d'activations de l'anticipation de la récompense, ainsi que d'explorer la connectivité fonctionnelle liée à la tâche chez les personnes saines, les personnes ayant une haute personnalité schizotypique et les personnes souffrant de schizophrénie. Dans ce but, tous les participants ont joué au MID tout en passant une IRMf. La personnalité schizotypique était évaluée à l'aide du questionnaire de la

personnalité schizotypique (SPQ) et les symptômes négatifs étaient évalués à l'aide de l'échelle brève des symptômes négatifs (BNSS).

Grâce à nos analyses, nous avons reproduit les anciens résultats sur les bases neuronales de l'anticipation de la récompense chez les personnes saines, démontrant une réactivité à la récompense dans le striatum ventral et dorsal, ainsi que dans des régions impliquées dans les réseaux moteurs et traitant la saillance. Nous avons aussi identifié le lien du striatum ventral avec les réseaux fonctionnels actifs dans la motivation, la motricité, l'attention et la vision pendant l'anticipation de la récompense. Ces résultats soutiennent l'hypothèse que le striatum ventral produit la saillance motivationnelle influençant les actions dirigées vers un but pour les stimuli récompensés. De plus, nous avons montré que les processus de l'anticipation de la récompense ne semblent pas impactés dans la personnalité schizotypique. Enfin, nos analyses ont confirmé la réduction de réactivité du striatum ventral dans la schizophrénie et son association avec l'apathie. Cependant, nous avons observé une grande variabilité dans les différentes cohortes de patients. Nous avons exploré ce qui pouvait expliquer cette variabilité et avons trouvé que les méthodes conventionnelles d'évaluation de l'anticipation de la récompense pourraient ne pas être assez spécifique pour saisir complètement l'association avec les symptômes négatifs. Nous avons de plus découvert que de hauts niveaux d'apathie sont associés avec des déficits de connexions dans le réseau de la saillance. Ces résultats supplémentent la recherche dans le domaine qui a montré des déficits globaux de connexion dans la schizophrénie.

En résumé, cette thèse a démontré que l'anticipation de la récompense est impactée différemment dans les différents niveaux du continuum de la psychose. L'évaluation des niveaux intermédiaires du continuum, tels que les individus classifiés comme Ultra Haut Risque (UHR) or ceux ayant vécu un Premier Épisode de Psychose (FEP), pourrait contribuer à définir le niveau précis durant lequel les déficits de l'anticipation de la récompense apparaissent.

3. Aims and Importance of This Research

"Why am I writing this thesis?" This question, which I have repeatedly asked myself for the last few months, seems to have a simple answer: "To get my diploma." This makes sense, doesn't it? Yet, it led me to another question: "Why am I doing a PhD in the first place?", to which I answered "To advance science." You might see a pattern emerge here. The questions of why we do things in our life is a great way to assess a core process of goal-directed behavior: motivation. Accordingly, a great part of our actions everyday seems to be motivated by the anticipation of rewards that are awaiting on the other side of those actions. So much so that, if we lose the capacity to properly anticipate these rewards, we might lose the motivation to do many of those everyday actions. This is what is believed to happen in patients with schizophrenia who have negative symptoms, and it is the subject I studied during the last five years.

The research I conducted during my PhD therefore aimed at refining our understanding of the neural processes underlying reward anticipation in participants on the psychosis continuum. The psychosis continuum offers two axes to classify pathologies in terms of symptoms, as well as in terms of severity. The axis used in this thesis describes symptom severity and includes three stages: health, schizotypy and schizophrenia (Johns & van Os, 2001; van Os, Hanssen, Bijl, & Ravelli, 2000).

The cortical and sub-cortical regions activated by reward anticipation in healthy participants have now been clearly defined (Knutson, Westdorp, Kaiser, & Hommer, 2000; Oldham et al., 2018; Wilson et al., 2018). Few studies have investigated activations during reward anticipation in schizotypy and results are inconsistent (Kirschner, Hager, Muff, et al., 2016; Yan et al., 2016). In contrast, deficits in reward anticipation have been previously demonstrated in schizophrenia, emphasizing ventral striatal activity as a marker of negative symptoms (e.g., Leroy et al., 2020; Radua et al., 2015; Yan et al., 2016). However, results on this matter have not always been conclusive either (e.g., Esslinger et al., 2012; Kirschner, Hager, Bischof, et al., 2016; Nielsen, Rostrup, Wulff, Bak, Broberg, et al., 2012). In addition, several papers have shown that ventral striatal activity during reward anticipation correlates with apathy, a dimension of negative symptoms, in schizophrenia (Kirschner, Hager, Muff, et al., 2016; Radua et al., 2015; Stepien et al., 2018). A replication of these results on larger samples of participants is therefore necessary to further consolidate our understanding of reward anticipation deficits in schizophrenia.

In comparison, while many studies evaluated resting state connectivity in participants of all stages of the psychosis continuum, no study has ever investigated functional connectivity during reward anticipation in adult healthy controls and individuals with high schizotypy. One study evaluated functional connectivity during reward anticipation in patients with schizophrenia and healthy controls with different degrees of subclinical symptom expression (Simon et al., 2015). There is therefore a whole area of research that needs to be explored in the psychosis continuum to help define these stages in greater details.

To respond to these problems, three main goals were set for my PhD: the replication of previous results on neural activity and an exploration of cortico-striatal networks underlying reward anticipation in 1) healthy participants, 2) individuals with high schizotypy and 3) patients with schizophrenia.

4. Introduction

4.1 Schizophrenia

Schizophrenia is a debilitating disorder that affects about 0.75% of the world population (Hilker et al., 2018; Moreno-Küstner, Martín, & Pastor, 2018). Despite its low prevalence compared to other disorders like depression and anxiety, schizophrenia has one of the highest median societal costs per patient among all psychiatric disorders (Christensen et al., 2020). This apparent discrepancy is due to several factors: first, the symptoms of schizophrenia often induce substantial impairments in social and professional contexts, which disrupt the entrance of patients into the work force. Second, symptoms usually appear in early adulthood (though up to 20% of patients develop symptoms and/or are diagnosed after turning 40; Maglione, Thomas, & Jeste, 2014; Suen et al., 2019) and therefore lead to lifelong difficulties. Third, patients with schizophrenia have a life expectancy reduced by at least 13 to 15 years compared to the general population (Hjorthøj, Stürup, McGrath, & Nordentoft, 2017). Fourth, patients with schizophrenia often have one or more psychiatric and physical comorbidities (e.g., anxiety, substance use disorder, diabetes, pneumonia; Lu et al., 2022). Finally, less than 20% of patients regain full cognitive and social capacities following the apparition of symptoms (Jääskeläinen et al., 2012). The combination of these factors strongly affects all facets of the adult life of patients with schizophrenia.

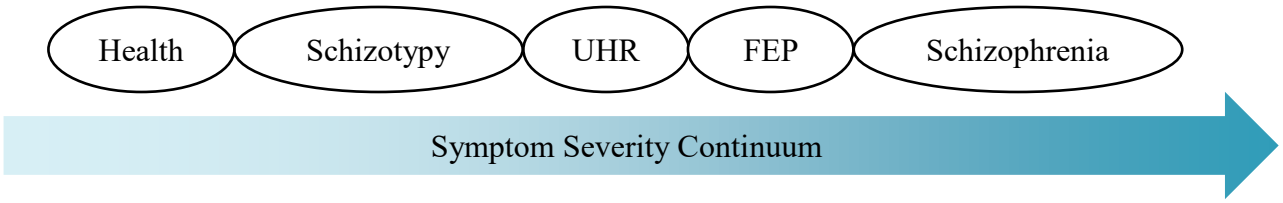

Figure 1. The different stages of the psychosis continuum in terms of symptom severity. Only health, schizotypy and schizophrenia are discussed in this thesis. UHR: Ultra-High Risk; FEP: First Episode Psychosis. Adapted from van Os et al. (2000).

Schizophrenia is defined through severely impairing positive, negative and cognitive symptoms ("Diagnostic and statistical manual of mental disorders—fifth edition: DSM-5," 2013). Positive symptoms define experiences added to normal human experience, such as hallucinations and disorganized thoughts. Conversely, negative symptoms represent a diminution of normal human experience and behavior, such as a lack of motivation and difficulty expressing oneself verbally and non-verbally. Finally, cognitive symptoms are characterized as impairments of cognitive functions, such as working memory and processing speed. Of note, all three categories of symptoms to diagnose schizophrenia were already present when Kraepelin characterized schizophrenia (1919).

To further complicate things, most of these symptoms are shared with other disorders, such as bipolar disorder, depression and anxiety. In addition, van Os et al. (2000) showed that subclinical psychotic symptoms such as benign hallucinations are experienced by a significant portion of the general population. These results led to the hypothesis of a psychosis continuum with one axis ranging across different degrees of symptom severity, which ranges from health to chronic schizophrenia and one axis ranging across different diagnoses, which includes for example depression, bipolar disorder, schizophrenia (Craddock & Owen, 2005; Johns & van Os, 2001; van Os et al., 2000; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). Note that from now on, all mentions of the psychosis continuum refer strictly to the symptom severity axis (Figure 1). Several stages within the continuum have been put forward, ranging from pre-clinical to clinical syndromes. These include health, schizotypal personality, ultra-high risk, first-episode psychosis and schizophrenia (Mennigen & Bearden, 2020). Each stage is associated with greater severity of symptoms. While interesting to characterize symptoms and their pathogenesis,

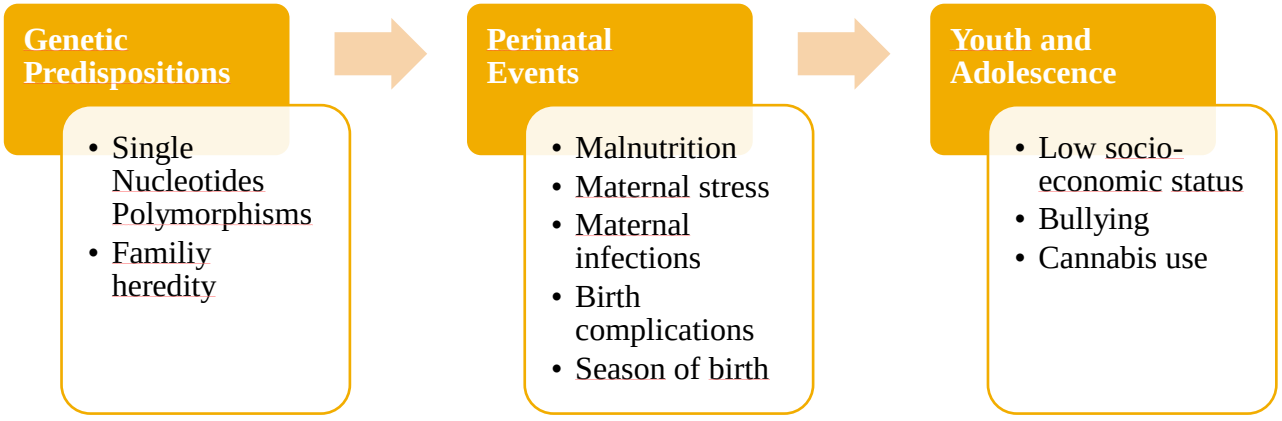

Figure 2. A summary of the inter-connected risk-factors underlined by modern neuro-socio-developmental theories by order of apparition.

several researchers have expressed doubts on the continuum's usefulness in clinical settings (Jauhar et al., 2021; Lawrie, Hall, McIntosh, Owens, & Johnstone, 2010).

The pathogenesis of schizophrenia is also highly heterogeneous and far precedes the symptoms' onset. Modern neuro-socio-developmental theories have underlined several factors in the pathology's development, emphasizing the interconnected roles of genetic and environmental risk factors (Figure 2). Schizophrenia has been linked to a complex set of genetic predispositions, with recent studies putting its heritability at 79% (Hilker et al., 2018). Single nucleotide polymorphisms on more than 100 loci (Ripke et al., 2014) and several rare copy number variants (Pocklington et al., 2015) have been identified. These variants are related to gene transcription problems possibly altering cell migration during brain development (Fromer et al., 2016), with modifications at pre- and post-synaptic locations (Trubetskoy et al., 2022) and with dopaminergic, glutamatergic (Ripke et al., 2014) and GABAergic neurotransmission changes (Pocklington et al., 2015). However, some of these risk genetic variants are pleiotropic with bipolar disorder and major depressive disorder mainly (Lee et al., 2013). Therefore, even though mounting results point towards genetic and neuro-developmental predispositions of schizophrenia, a clear definition of these factors remains difficult.

The delineation of genetic causes is further complicated by the influence of environmental factors in the development of symptoms. First, neuro-socio-developmental hypotheses include perinatal risk factors of schizophrenia. Malnutrition, maternal stress, maternal infections and

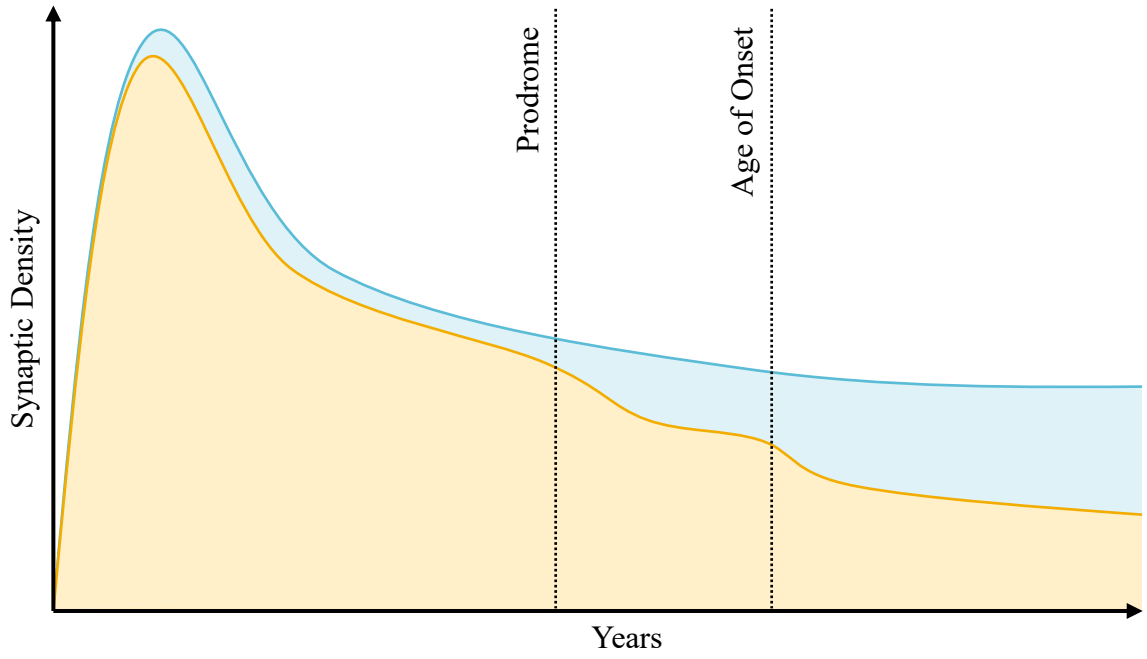

Figure 3. A representation of synaptic density in healthy individuals (blue) and patients with schizophrenia (yellow). Increased synaptic pruning in schizophrenia has been hypothesized to cause exitatory/inhibitory imbalance. Adapted from Howes & Shatalina (2022).

birth complications have been identified in cohort studies (Davies et al., 2020; Hulshoff Pol et al., 2000). Season of birth is another well-known perinatal risk factor, with children born during the late winter and early spring months being more at risk (Davies, Welham, Chant, Torrey, & McGrath, 2003).

Socioeconomic factors can further increase the risk of developing schizophrenia. For example, first- and second-generation immigrants have a higher prevalence of schizophrenia than natives (Cantor-Graae & Selten, 2005; Eger et al., 2022). Growing up with a low socio-economic status also constitutes a risk factor (Hakulinen, Webb, Pedersen, Agerbo, & Mok, 2020; Schneider, Müller, & Knies, 2022). Finally, although a causal link has yet to be demonstrated, cannabis use is linked to an increased risk of developing schizophrenia, in particular during adolescence (Gage, Hickman, & Zammit, 2016). In summary, the interplay between genetic and environmental factors constitutes the most potent risk for the development of the disorder and the apparition of symptoms.

At the cerebral level, this interplay can cause structural and functional deficiencies. Schizophrenia has been associated with lower synaptic density due to increased synaptic pruning (Figure 3), especially in the frontal lobe, in post-mortem (Berdenis van Berlekom et al., 2019) and in vivo studies (Radhakrishnan et al., 2021). Patients with schizophrenia also show lower gyrification (Zakharova et al., 2021) and lower grey matter volume, especially in frontal regions (Cropley et al., 2016). Functionally, an imbalance between excitatory and inhibitory processes has been described. In humans, this imbalance is assessed as excess gamma-band power during resting-state EEG (Grent-'t-Jong et al., 2018). Such an imbalance could originate from aberrant synaptic pruning of GABAergic and glutamatergic synapses (Feinberg, 1982). Additionally, animal models show that environmental factors like prenatal stress can also cause such an imbalance (Marchisella et al., 2021).

The development of positive symptoms is also thought to depend on the dopaminergic system (although several other neurotransmitters, including serotonin and glutamate, are investigated; Stahl, 2018). Dopamine is a neurotransmitter necessary for motor, motivation and cognitive functions. Positive symptoms have been associated with excess dopamine synthesis and release in the striatum (Howes et al., 2012) and all current antipsychotic drugs treating positive symptoms are mostly dopamine partial agonists or antagonists (Kaar, Natesan, McCutcheon, & Howes, 2020).

4.2 Negative Symptoms

Conversely, the biological underpinnings of negative symptoms are not yet fully understood. One hypothesis stipulates that hyperdopaminergic striatal activity might also hinder transient firing for relevant stimuli, a deficiency that could translate into negative symptoms (Maia & Frank, 2017). Yet, negative symptoms usually do not strongly benefit from treatments targeting the dopaminergic system (Németh et al., 2017). Several other pharmacological candidates have been explored, such as sigma-2, serotonin (Davidson et al., 2017) and glutamate (Tuominen, Tiihonen, & Wahlbeck, 2005), all leading to at best moderate improvements in clinical studies. Recent guidance on treatment from the European Psychiatry Association promotes the use of second-generation antipsychotics, with antidepressant add-ons and social skills trainings (Galderisi et al., 2021). The difficulty to find appropriate treatments strongly depend on our

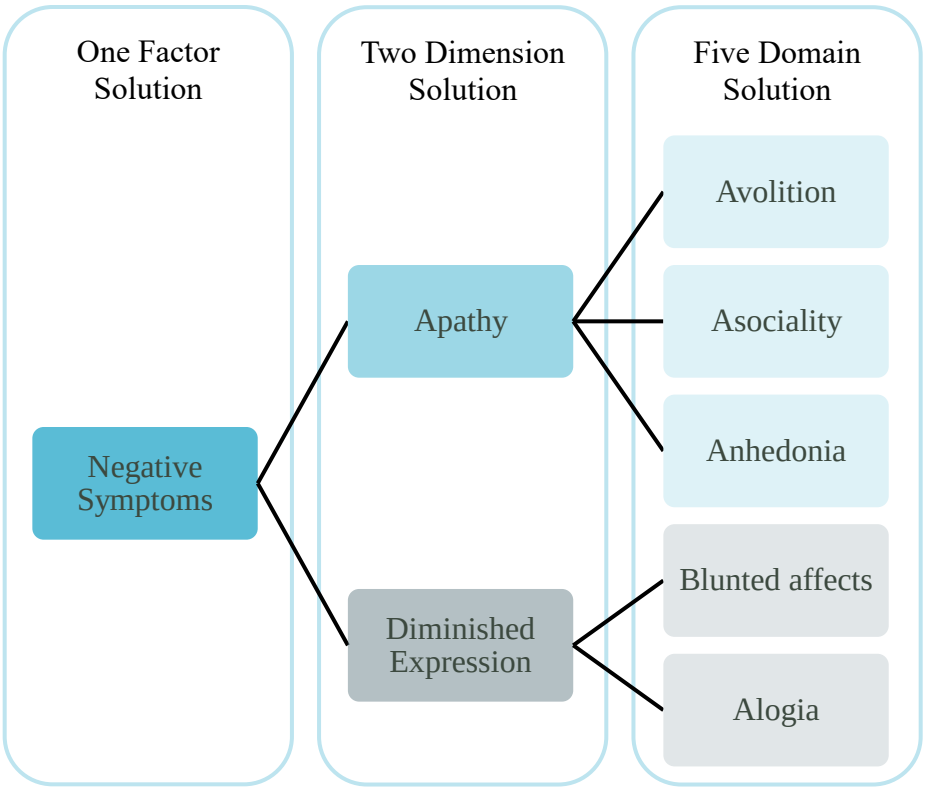

Figure 4. Representation of the one factor, two dimension and five domain solutions of negative symptoms. Adapted from Kaliuzhna et al. (2021).

understanding of the chemical causes of negative symptoms. However, research in this field has also been hindered by problems regarding the evaluation of negative symptoms themselves.

Accordingly, one major difficulty involves discriminating between primary negative symptoms and secondary negative symptoms (Möller, 2007). While primary symptoms are intrinsic to the disorder, secondary symptoms are side effects of primary positive symptoms, extrapyramidal symptoms and other pathologies like depression (Carpenter, Heinrichs, & Alphs, 1985; Kirkpatrick et al., 2011). Evaluating symptoms across several time points can help, as secondary negative symptoms usually decrease when their cause is treated. However, primary negative symptoms can co-exist with secondary negative symptoms, and other pathologies with similar symptoms like depression. Specific scales like the Brief Negative Symptom Scale (Kirkpatrick et al., 2011) therefore need to be used in conjunction with scales assessing possible sources of secondary negative symptoms (e.g., the Positive And Negative Syndrome Scale for the evaluation of positive symptoms; Kay, Fiszbein, & Opler, 1987).

Additionally, negative symptoms are not themselves a homogeneous concept. The NIMH-MATRICS consensus defined five intercorrelated domains of negative symptoms (Figure 4; Kirkpatrick, Fenton, Carpenter, & Marder, 2006). Avolition refers to the reduced motivation and energy to partake in everyday activities. Asociality refers to the diminution of social behaviors and the motivation to engage in social activities. Anhedonia refers to the reduced intensity, frequency and expectation of pleasure in everyday activities. Blunted affect refers to the reduction of expressed emotions. Alogia refers to deficits in speech qualities such as speed, volume and quantity. A robust clinical and physiological understanding of these domains is critical since their time-course and functional impact widely vary. Accordingly, asociality appears before the acute psychosis event (Tarbox & Pogue-Geile, 2008) and can predict the disease outcome (Marchesi et al., 2015), whereas avolition, asociality and anhedonia are more prevalent in early psychosis patients than positive symptoms (Lyne et al., 2015). Thus, having specific markers to detect them early is crucial to help target individuals at high risk of developing schizophrenia.

These five symptom domains have been shown to load on two dimensions: apathy and diminished expression (Kaiser et al., 2017; Kaliuzhna et al., 2021; Kirkpatrick et al., 2011; Messinger et al., 2011). The apathy dimension regroups anhedonia, asociality and avolition and refers to the difficulty in experiencing pleasure and reduced goal-directed and motivated behaviors. The diminished expression dimension includes blunted affect and alogia and refers to reduced emotional and speech productions. These dimensions differentially influence measures of functional outcome, illness development and subjective quality of life. Accordingly, patients with schizophrenia with higher apathy had more gradual onsets of psychosis, decreased social skills before the onset of the disorder, more severe thought disorder, fewer chances to be employed and more significant impairments in work and school occupations (Strauss, Horan, et al., 2013).

Despite the prevalence and the socioeconomic impact of negative symptoms on patients, early detection and effective treatments are still eluding researchers. This prompts the need for marker candidates that could help with the diagnostic of negative symptoms and define specific targets for treatments. Accordingly, the two dimensions of negative symptoms do not rely on the same cognitive processes and are associated with different neural dysfunctions. While there is no

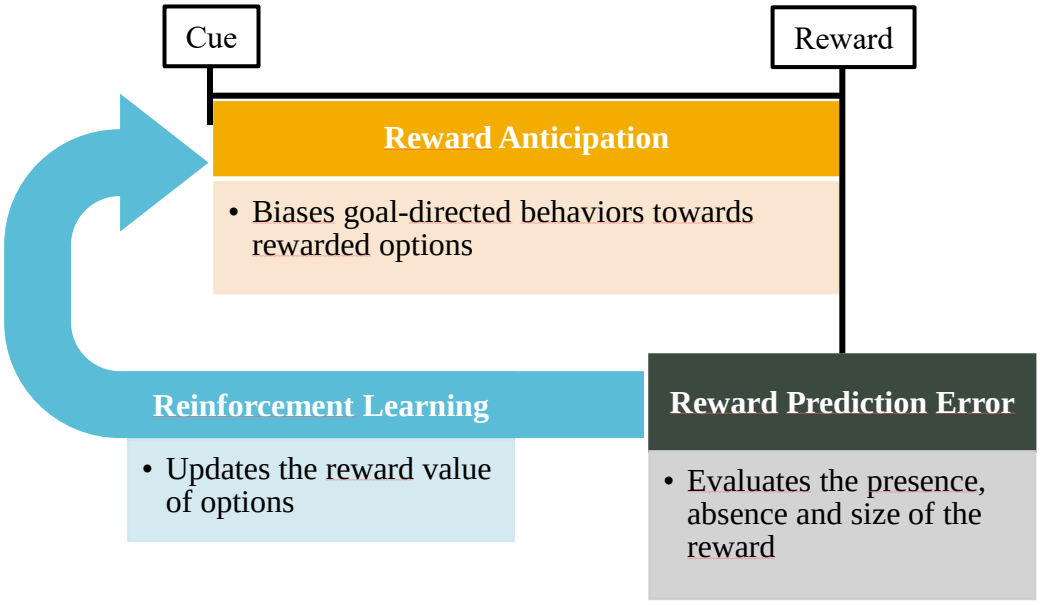

Figure 5. A representation of three processes at play to produce motivation. Reward anticipation starts at the presentation of a cue and attributes motivational salience to rewarded options to bias goal-directed behaviors towards them (Knutson et al., 2000). During reward consumption, reward prediction error evaluates the presence, absence and size of rewards (Schultz, 2016). Reinforcement learning updates the reward value of options to modulate reward anticipation of future events (Averbeck & O'Doherty, 2022).

consensus on cognitive models or neurobiological bases underlying diminished expression, apathy is thought to arise from motivational impairments (Strauss, Waltz, & Gold, 2013).

4.3 Motivation

Motivation is a process (or range of processes) that helps humans and other animals to perform goal-directed behaviors. When faced with the choice to act, costs and benefits tied to said action are weighted (Salamone, 1992; Salamone, Yohn, López-Cruz, San Miguel, & Correa, 2016). Costs comprise, for example, the estimation of the effort necessary to act (Gold et al., 2013; Hartmann et al., 2014). Conversely, benefits can be divided into intrinsic and extrinsic categories (Deci, 1971). Intrinsic incentives represent hedonic or reward responses induced by the action (e.g., performing an action solely because one enjoys it). On the contrary, extrinsic incentives are not part of the action and are often given after the action is performed. Extrinsic incentives can

be further divided into two categories: inherent incentives that fulfil biological needs (e.g., food, water) and incentives whose value has to be learnt (e.g., money). Confronting the costs and the incentives of future actions will help decide if these actions will be undertaken, but also how much energy to allocate to the body to start and sustain them (Nevid, 2012).

Several interdependent motivational processes take part in the formation of goal-directed behaviors (Figure 5). Reinforcement learning relates to the acquisition of the association between a reward and an action, effectively giving that action a unique value. The decision to perform a specific action amongst an array of different behaviors will then be based on the action with the higher value (i.e., the higher chance to give a reward.) Reinforcement learning mostly activates neuronal networks connecting the striatum and the prefrontal cortex (Averbeck & O'Doherty, 2022). The acquisition and modulation of the value created by reinforcement learning is moderated by reward prediction error and reward anticipation processes. Reward prediction error evaluates the presence or absence of a reward and its size based on the expected reward that this action should deliver. To do so, prediction error uses phasic firing of dopaminergic neurons from the ventral tegmental area and substantia nigra (Nasser, Calu, Schoenbaum, & Sharpe, 2017; Schultz, 1998; Schultz, 2016). While prediction error is computed during the reward consumption, reward anticipation happens before the action selection.

4.4 Reward Anticipation

Correctly anticipating incentives represents a fundamental component of approach behaviors. The Monetary Incentive Delay (MID) task has often been used to assess reward anticipation, as it follows a procedure simple enough to be performed by patients (Knutson et al., 2000). The MID starts by giving participants a cue indicating the amount of money they can win per trial. Then, participants perform a discrimination task. In the MID, reward anticipation is modelled as the time between the cue and target presentations.

The MID assesses both behavioral and neural correlates of reward anticipation. In fMRI studies on healthy controls, reward anticipation reliably activates cortical and subcortical regions. The ventral striatum holds a central role in this system, as it calculates the subjective value of future incentives, or motivational salience (Filimon, Nelson, Sejnowski, Sereno, & Cottrell, 2020; Knutson et al., 2000; Williams et al., 2021). This process is thought to rely on a shift of phasic dopamine release in the striatum from the moment of reward consumption to the moment reward

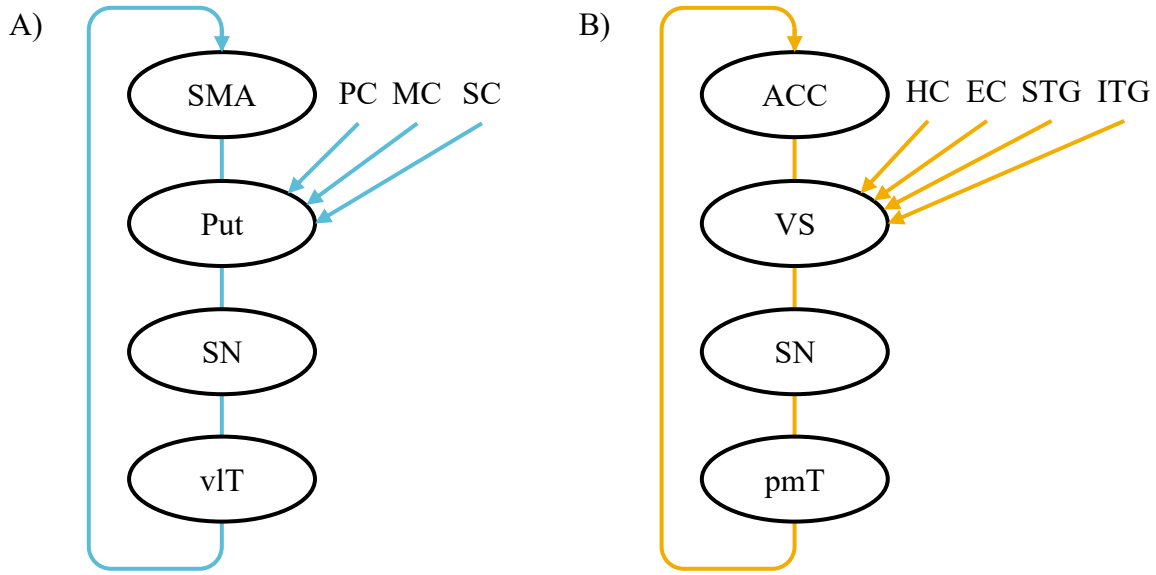

Figure 6. Examples of cortico-striatal networks as described by Alexander et al. (1986), including the motor (A) and salience (B) networks. Regions of the motor network include the supplementary motor area (SMA), putamen (Put), substantia nigra (SN), ventralis lateralis pars oralis and medialis thalamus (vlT), premotor cortex (PC), motor cortex (MC) and somatosensory cortex (SC). Regions of the salience network include the anterior cingulate cortex (ACC), ventral striatum (VS), SN, posteromedial medialis dorsalis thalamus (pmT), hippocampus (HC), entorhinal cortex (EC), superior temporal gyrus (STG) and inferior temporal gyrus (ITG).

is anticipated (e.g., when a cue indicating a future reward is presented; Berridge & Robinson, 1998; Schott et al., 2008; Schultz, 1998, 2002).

Reward anticipation also relies on the dorsal striatum. The dorsal striatum is thought as a middle man between the reward networks and motor networks. As such, it integrates ventral striatal activation in order to perform the most appropriate action selection (Balleine, Delgado, & Hikosaka, 2007; Oldham et al., 2018). The anterior cingulate cortex and anterior insula are both part of the salience network and help feed reward information to the attentional network to orient it towards rewarded actions and stimuli (Rothkirch, Schmack, Deserno, Darmohray, & Sterzer, 2014; Schneider, Leuchs, Czisch, Sämann, & Spoormaker, 2018). The orbitofrontal cortex has

also been brought forth as a region of interest for optimal anticipation (Kahnt, Heinzle, Park, & Haynes, 2010), though its role within reward anticipation is still debated (Oldham et al., 2018). Behaviorally, motivational salience, paired with motor preparation and biased attention, is thought to lead to faster responses to task trials leading to high rewards compared to trials associated with no reward, a concept coined as reward-related speeding, or, more simply, response time speeding (e.g., Kirschner, Hager, Bischof, et al., 2016).

Of note, all of these regions are part of cortico-striatal networks known to regulate and be regulated by dopamine activity and modulating motivational processes (Figure 6; Alexander, DeLong, & Strick, 1986; Haber, 2016). Yet, no study has ever investigated how these networks activate during reward anticipation in healthy participants. Additionally, functional connectivity has been brought forward as a bearer of possible additional neural markers in mental disorders (Zhang et al., 2021). Therefore, a clear understanding of healthy task-based cortico-striatal functional connectivity is necessary to define which networks underlie healthy reward anticipation and how these networks are affected in mental disorders.

4.5 Reward Anticipation Impairments in Disorders of the Psychosis Continuum

Accordingly, the motivational impairments in disorders of the psychosis continuum have been thoroughly studied in the last two decades. Reward anticipation deficits, in particular, have been described in patients with schizophrenia (e.g., Kirschner, Hager, Bischof, et al., 2016; Radua et al., 2015). In patients with schizotypal personality, deficits seem more present in sub-groups of patients with high negative symptoms (Yan et al., 2016). Behaviorally, impaired reward anticipation leads to smaller response time speeding (e.g., Esslinger et al., 2012; Stepien et al., 2018), though not all studies found such a decrease (e.g., Kirschner, Hager, Bischof, et al., 2016).

At the neural level, deficits in reward anticipation in schizophrenia have been associated with decreased ventral striatal activity in several meta-analyses mostly focusing on the MID (Juckel et al., 2006; Leroy et al., 2020; Radua et al., 2015; Zeng et al., 2022), though other tasks led to similar results (Chase, Loriemi, Wensing, Eickhoff, & Nickl-Jockschat, 2018). Decreased ventral striatal activity contrasts with the hyperdopaminergia present in schizophrenia, as ventral striatal activity correlates with dopamine release (Schott et al., 2008). However, it is important to note that reward anticipation is modelled by subtracting the No Reward condition from the High

Reward condition. By doing so, the baseline activity of the regions of interest is taken out to assess the specific effect of reward on those region's activity. However, a decrease in activity during reward anticipation could relate to an increase in activity for the No Reward condition or a decrease of activity from the High Reward condition. Accordingly, computational theories attribute reward anticipation deficits to a decrease in adaptive dopaminergic transients (Maia & Frank, 2017). Yet, these deficits could come from a reduction of adaptive transients, or from difficulties to differentiate adaptive transients from spontaneous transients induced by the hyperdopaminergia, or both (Roiser et al., 2009).

In schizotypy, ventral striatal activity is preserved during reward anticipation (Kirschner, Hager, Muff, et al., 2016; Yan et al., 2016), though Yan et al. (2016) found a decrease in ventral striatal activity in participants showing mainly negative symptoms. Accordingly, pre-clinical individuals on the psychosis continuum show similar levels of striatal dopamine compared with healthy controls (McCutcheon, Merritt, & Howes, 2021). The emergence of ventral striatal deficits in the psychosis continuum could therefore be related to the apparition of striatal hyperdopaminergia.

In schizophrenia, ventral striatal activity during reward anticipation has been shown to correlate negatively with negative symptoms (Dowd & Barch, 2010; Kirschner, Hager, Bischof, et al., 2016; Radua et al., 2015; Simon et al., 2015; Stepien et al., 2018; Waltz et al., 2010), though several studies did not find this relationship and found an association with positive symptoms instead (Esslinger et al., 2012; Nielsen, Rostrup, Wulff, Bak, Lublin, et al., 2012). When looking at the two dimensions of negative symptoms, several studies have found that deficits in reward anticipation specifically correlate with apathy and not diminished expression (Kirschner, Hager, Bischof, et al., 2016; Radua et al., 2015; Stepien et al., 2018). These results prompted the hypothesis that apathy, but not diminished expression, arises from motivational impairments schizophrenia and that ventral striatal deactivation could be used as a neural biomarker of motivational negative symptoms.

However, to serve as a biomarker in clinical trials, ventral striatal deactivation still needs to fulfill two supplementary criteria. First, the results need to be reproducible across sites to be generalizable to large scale cohorts. Then, the results need to be stable over time, meaning that ventral striatal activity should fluctuate together with apathy severity over time. Of importance, additional studies found that dorsal striatal and dorsolateral prefrontal cortex activities have also

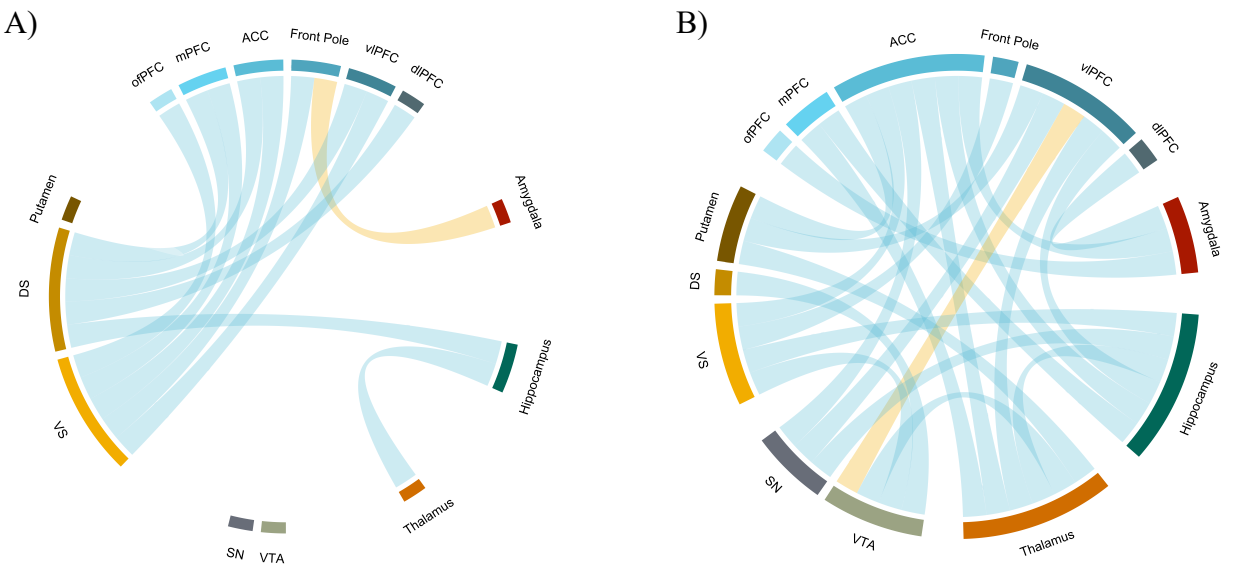

Figure 7. Patterns of whole-brain hypoconnectivity (blue) and hyperconnectivity (yellow) in schizotypy (A) and schizophrenia (B). Regions include the orbitofrontal prefrontal cortex (ofPFC), medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), front pole, ventrolateral prefrontal cortex (vlPFC), dorsolateral prefrontal cortex (dlPFC), amygdala, hippocampus, thalamus, ventral tegmental area (VTA), substantia nigra (SN), ventral striatum (VS), dorsal striatum (DS) and putamen. Adapted from Sabaroedin, Tiego et al. (2023).

been shown to correlate with negative symptoms (Dowd, Frank, Collins, Gold, & Barch, 2016; Mucci et al., 2015; Stepien et al., 2018), indicating that other subcortical targets could represent potential biomarkers.

Another potential neural marker of the psychosis continuum comes from cortico-striatal functional connectivity research. Accordingly, resting state functional connectivity analyses have shown patterns of hypo- and hyper-connectivity in all stages of the continuum (Figure 7). For example, individuals with high schizotypal traits have shown decreased fronto-striatal (Wang et al., 2021) and temporo-striatal functional connectivity (Kozhuharova, Saviola, Diaconescu, & Allen, 2021). Schizophrenia has also been linked with widespread cortico-striatal dysconnectivity (Fornito et al., 2013; Li et al., 2016; Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011; Sabaroedin, Tiego, & Fornito, 2023), with an emphasis on fronto-striatal

hypoconnectivity. Additionally, dysconnectivity patterns in schizophrenia have been shown to correlate with negative symptoms (Brakowski et al., 2020; Shukla et al., 2018; Tian, Zalesky, Bousman, Everall, & Pantelis, 2019; Wang et al., 2016). As mentioned earlier, cortico-striatal networks play a critical role in dopamine activity modulation and could therefore play a part in the hyperdopaminergia present in schizophrenia. To our knowledge, only one study ever assessed task-based functional connectivity in schizophrenia (Simon et al., 2015) and none in healthy individuals with high schizotypal traits. Yet, a clear understanding of how these dysconnectivities affect specific processes such as reward anticipation in all stages of the continuum could help characterizing their involvement in the development of symptoms.

4.6 Open Questions

In summary, we know that reward anticipation robustly activates the striatum, as well as regions of the cortex dealing with salience, attention and motor preparation. Schizotypy has been associated with ventral striatal deficits during reward anticipation, though the association is weaker. On the other hand, schizophrenia has repeatedly been associated with a decrease in ventral striatal activity and this activity has been shown to correlate with apathy in several studies. Finally, all stages of the psychosis continuum have been associated with various degrees of patterns of resting-state cortico-striatal dysconnectivity. Three groups of research questions can therefore be formulated and will be assessed in this thesis:

1) Are previous activation results during reward anticipation in healthy controls reproducible? What does healthy functional connectivity during reward anticipation looks like? We hypothesized that 1) we would find regions responding to reward anticipation already described in previous studies; and 2) cortico-striatal functional connectivity analyses would uncover links between the ventral striatum to regions of the salience, attention and motor networks. Accordingly, such networks should work conjointly to propagate motivational salience and bias goal-directed behaviors towards rewarded actions.
2) Is reward anticipation impaired in pre-clinical stages of the psychosis continuum, like schizotypy? Despite inconclusive previous results, we hypothesized that individuals with high schizotypy would show deficits in reward anticipation similar to those present in

schizophrenia. We expected to find decreased ventral striatal activity and patters of hypo- and hyper cortico-striatal functional connectivity.

3) Finally, are deficits during reward anticipation in schizophrenia reproducible? Does the ventral striatum qualify as a potential biomarker for apathy in schizophrenia? Can task-based functional connectivity patterns be used as biomarkers of schizophrenia and more specifically of apathy? Our hypotheses were that 1) we would find decreased ventral striatal activity in patients with schizophrenia and that this activity would correlate with apathy; 2) that these results would be stable across sites and over time; and 3) that patterns of functional dysconnectivity would be present in schizophrenia and also correlate with apathy.

5. Methods

5.1 Clinical Assessment

The Brief Negative Symptom Scale (BNSS; Kirkpatrick et al., 2011; Strauss et al., 2012) is a clinical tool that uses a semi-structured interview by clinicians to evaluate negative symptoms in schizophrenia. This scale was developed in response to analyses that found previous scale not sensitive enough to the complexity of negative symptoms. The BNSS measures the two dimensions and five domains of negative symptoms described above. The scale has 13 items scored on a 7-point scale. The BNSS is valid, reliable and sensitive to changes in negative symptoms over time, making it a prime tool to evaluate negative symptoms in our studies.

The Self-evaluation of Negative Symptom scale (SNS; Dollfus, Mach, & Morello, 2016) is a self-report assessment tool. The SNS relates to the self-experience of negative symptoms, which is not assessed by the BNSS. This tool includes 20 items scored on a 5-point scale. The SNS scores can also be used to assess the two dimensions and five domains of negative symptoms described above.

Schizotypal personality was assessed in healthy individuals using the Schizotypal Personality Questionnaire (SPQ; Raine, 1991). The SPQ was designed to assess behaviors, thoughts and feelings similar to those found in individuals with schizophrenia. The scale includes 74 items rated on a 5-point scale. The SPQ scores evaluate nine domains of schizotypal personality that are thought to represent three broader dimensions: cognitive-perceptual deficits (sometimes interpreted as positive symptoms), interpersonal deficits (sometimes interpreted as negative symptoms) and disorganized behavior.

In addition, several scales were used in our studies to evaluate causes for secondary negative symptoms. These scales were therefore used as criteria for the participants' inclusion. We used the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), which assesses the severity of positive, negative and general symptoms in patients with schizophrenia. In our case, we used it to exclude participants with symptoms that scored above 4 on any item of the positive sub-scale. Extrapyramidal symptoms were evaluated with the St. Hans Rating Scale (SHRS; Gerlach et al., 1993). Depression was evaluated with the Calgary Depression Scale (CDS; Addington, Addington, & Maticka-tyndale, 1993). Additionally, we used the Mini-International

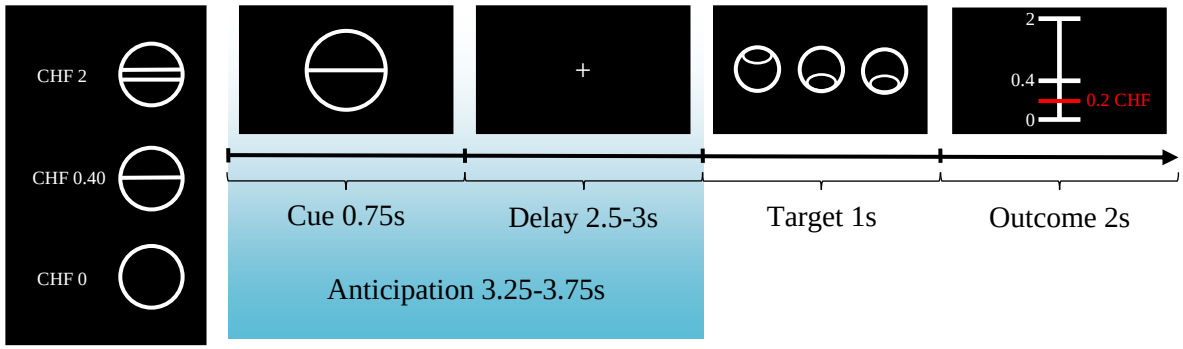

Figure 8. The Monetary Incentive Delay (MID) task. In this task, reward anticipation is modeled as the time between the presentation of the cue and the presentation of the target.

Neuropsychiatric Interview (MINI; Sheehan et al., 1998) from the DSM-IV to exclude participants with Axis I disorder comorbidities.

5.2 Experimental Design

Since all three papers presented in this thesis used the MID to assess the neural underpinnings of reward anticipation, a thorough description of the task and related analyses is given here. We used a version of the MID developed by Knutson et al. (2000) and modified by Simon et al. (2015; Figure 8). All trials started with a cue (0.75s) presented at the site of the screen. The cues represented the maximum amount of reward that participants could earn per trial (No Reward condition: 0CHF/0EUR; Low Reward condition: 0.40CHF/0.20EUR; High Reward condition: 2CHF/1EUR). A short delay (2.5 to 3s) led to the discrimination task where participants had to find an incongruent target among an array of three circles (1s maximum). The next screen gave participants feedback on their performance and, in case of a correct answer, indicated the amount of reward won for that trial. Finally, an intertrial interval represented by a fixation cross was presented (jittered between 1 and 9s, with a mean of 3.5s). The task comprised a training session outside the scanner (12 trials, 2 minutes in total), a training session inside the scanner (6 trials, 1 minute in total) to get used to the fMRI answer boxes, and two test sessions inside the scanner (36 trials and 6 minutes each).

The MID was modified by Simon et al. (2015) to adapt to the participant's performance. In this version, the amount of reward per trial is calculated as a percentage of the maximum amount based on the response time in the previous 15 trials. This is particularly important when testing

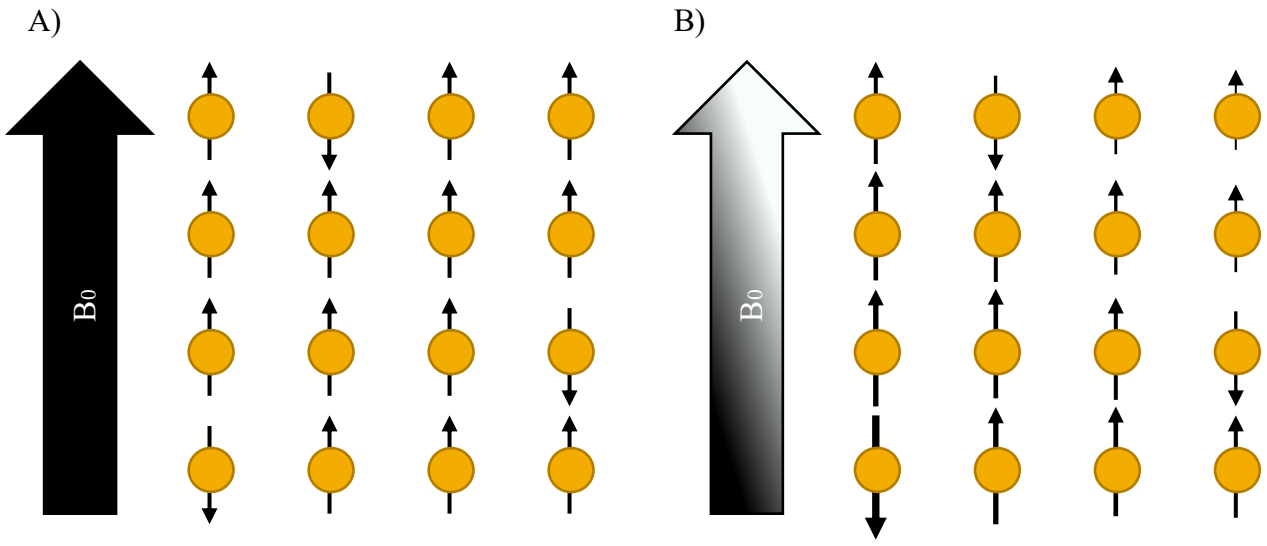

Figure 9. A) Hydrogen atoms in B_0. All spins are aligned with the same magnetic field. Some spins are reversed. B) B_0 is modified with a gradient along both axes. The magnetic field becomes strongest at the bottom left and weakest at the top right.

patients with schizophrenia, as they are on average slower than controls. With this technique, we ensured similar amounts of reward at the end of the experiment. Note that the performance to the first 15 trials (i.e. during the training sessions outside and inside of the scanner) are calculated using an array of 15 response time acquired during a pilot study.

5.3 Behavioral Analyses

Response time was defined as the time between target presentation and button press. Response time speeding was calculated by subtracting the mean No Reward response time to the mean High Reward response time. Group differences were assessed using repeated-measure ANOVAs with Group (SZ versus HC) as the between-subject factor and Reward (No, Low, High) as the within-subject factor.

5.4 fMRI Analyses

Magnetic resonance imaging (MRI) uses magnetic fields and radio waves to image the different tissues of the body (Brown, Cheng, Haacke, Thompson, & Venkatesan, 2014). First, the application of a strong magnetic field (usually referred to as B_0) aligns of the spins of hydrogen atoms in water molecules that usually orient at random (Figure 9). A gradient field is added to B_0

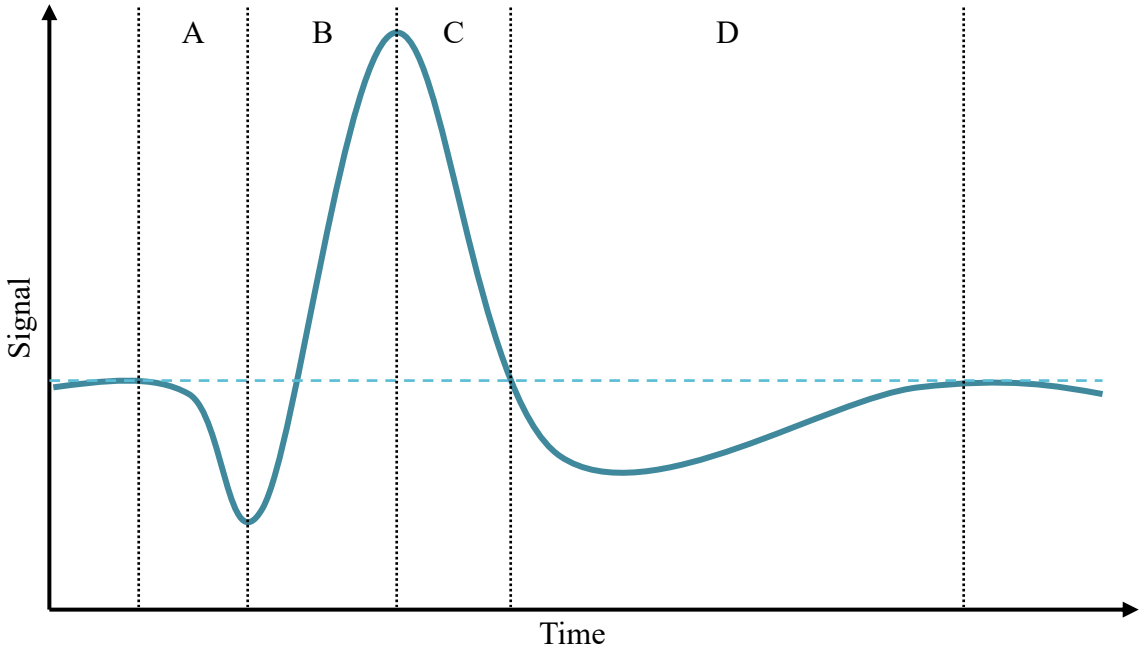

Figure 10. The hemodynamic response for a short burst of neural activity. A) The region starts consuming oxygen with no influx of oxyhemoglobin, the ratio of deoxyhemoglobin over oxyhemoglobin increases. B) The influx of oxyhemoglobin starts, leading to a reduction and inversion of the ration until the peak. C) The influx of oxyhemoglobin stops, leading to a reduction of the ratio. D) Overshoot of the consumption of oxygen until the system stabilizes back to equilibrium.

so that the orientation of the spins is location-dependent in all three orthogonal directions. Sending a radio wave then destabilizes the alignment of the hydrogen atoms in B_0. As the spins relax back to B_0, they emit nuclear magnetic resonance signal (NMR), which can be measured using antennas within the MRI machine. Through a reversed Fourier transform, the signal can then be mapped into an image of the body, or, in our case, the brain. Since the various tissues of the brain (e.g., grey matter, white matter, cerebrospinal fluid) have different water content (or proton density), the signal they emit can be differentiated, making them visibly distinct in MRI images.

Functional MRI (fMRI) aims at using the MRI properties to image brain activity over time (Logothetis, 2008). The main disadvantage of MRI is that the acquisition of data is slow compared to the speed of neural activity. Researchers bypassed this problem by taking advantage

of the magnetic properties of blood. Their rationale is that activated brain cells consume glucose and oxygen. Therefore, if a region of the brain is activated by an event, the blood flow to this region will increase to respond to the increased demand in glucose and oxygen. Interestingly, deoxyhemoglobin (i.e. hemoglobin not attached to an oxygen atom), a paramagnetic metalloprotein, acts as an endogenous contrast agent in MRI analyses (i.e. the presence of deoxyhemoglobin disrupts the NMR signal and induces signal loss) and becomes diamagnetic when attached to oxygen atoms. fMRI therefore images the changes in the ratio of oxyhemoglobin and deoxyhemoglobin over time (or Blood Oxygenation Level Dependent effect, BOLD) as a proxy of cerebral activity. An example of what this hemodynamic response looks like can be found in Figure 10.

Once the NMR signal has been acquired, the data has to be preprocessed to be comparable between participants and to increase the signal-to-noise ratio. The main steps include motion correction, slice timing correction (i.e. correcting for the fact that the whole brain is not acquired at one single time point, but through several slices), spatial normalization (i.e. bringing all images in the same space) and smoothing (i.e. using a Gaussian filter to reduce the impact of scanner and physiological noise). The goal is then to create a model based on the convolution of study parameters and the canonical hemodynamic response function. Researchers then fit the model to the signal extracted from each voxel. Voxels that show the best fit are then interpreted as showing task-related activity.

5.4.1 First Level Definition

In our case, we created a general linear model (GLM, Figure 11) on SPM using 12 regressors in total. These regressors represent the task events are convoluted with a canonical hemodynamic response function. Three regressors for the anticipation phase and three regressors for the consumption phase (No Reward, Low Reward, High Reward). The Low Reward and High Reward consumption regressors were parametrically modulated by the actual reward amount won per trial. One regressor modeled target presentation. Three regressors modeled error trials in the anticipation, target and consumption phase. We used the canonical hemodynamic function to convolve the 12 regressors. The contrasts of interest from first level analyses included the No Reward, Low Reward, High reward regressors from the anticipation phase. Reward anticipation was assessed by looking at the [High Reward > No Reward] contrast.

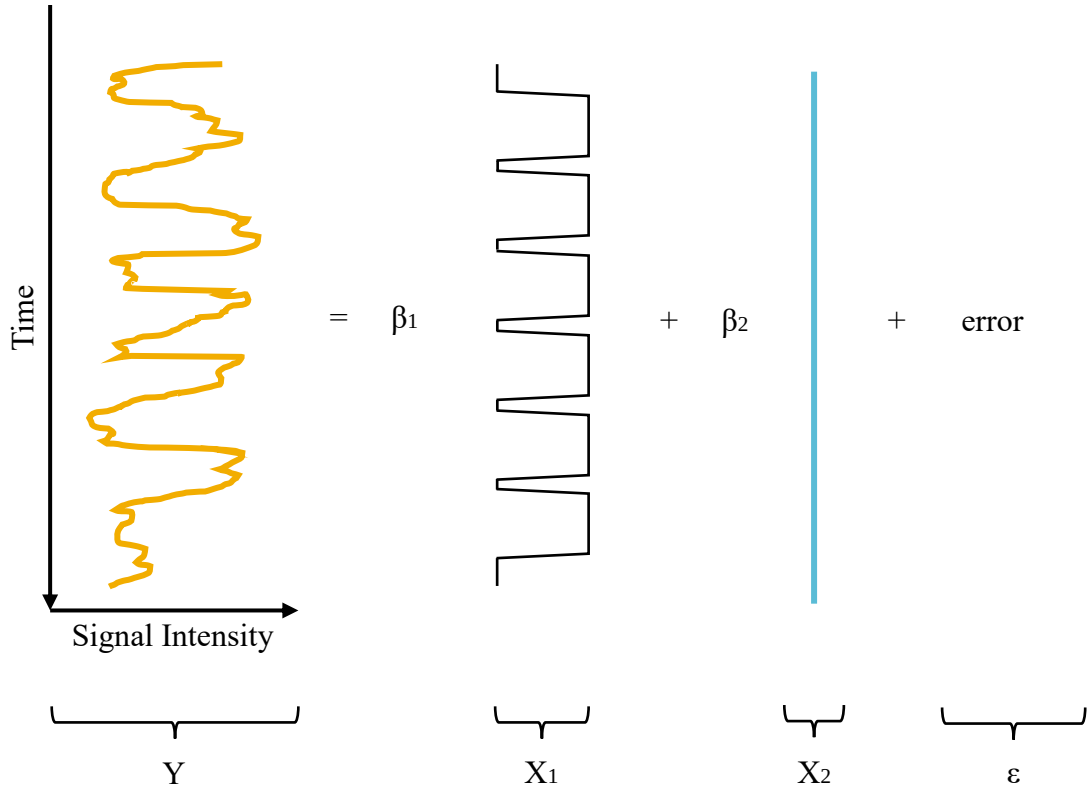

Figure 11. Illustration of the General Linear Model (GLM) used in fMRI analyses. At least one experimental condition vector (X_1) and a constant (X_2) are multiplied by β weights that have to be solved for. An error term (ε) is added. Once the GLM is created, we can convolve the HRF with it to create the model with which we are going to fit the signal from each voxel of interest. Adapted from Monti (2011).

5.4.2 Second Level Definition

Whole-brain activation analyses were performed on SPM using one-sample t-test to investigate reward anticipation in groups taken separately and two-sample t-tests to assess group differences. ROI responsivity betas from the contrast of interest [High Reward > No Reward] were extracted from two-sample t-tests using Marsbar and were fed in mixed models with Group (SZ versus HC), Site (CH versus GE) and Session (Session 1 versus Session 2) as between-subject factors and Participants as the random effect.

ROI activation betas from single regressors (No reward, Low Reward and High Reward) were extracted from two-sample t-tests using Marsbar for supplementary analyses. Note that fMRI

analyses based on single regressors invariably include activity related to processes unrelated to the functions we want to assess. Such results should therefore be interpreted with caution.

5.4.4 Psychophysiological Interaction Analyses (PPI)

Functional connectivity analyses were performed using the PPI toolbox from SPM (Friston et al., 1997). The idea behind functional connectivity is that two brain regions that are functionally related will show similar patterns of activity in relation to a task. PPI analyses formalize this idea through three steps: First, a seed region of interest (ROI) is defined. Then, time series data are extracted from the seed and from all either whole-brain voxels, or specific ROIs believed to work conjointly with the seed. Finally, we calculate the psychophysiological interaction effect by multiplying the seed's time series data by the vector representing the experimental condition task (i.e. the psychological factor). Then, we assess how this multiplication affects the correlation between the seed ROI and other brain regions.

In our analyses, connectivity maps during reward anticipation were assessed using the left ventral striatum and right ventral striatum as separate seeds. The contrast of interest [High Reward > No Reward] represented the psychological factor. Three PPI regressors (Interaction, Seed activity and Psychological regressor) were modelled in GLM for each participant. Whole-brain group comparison were then performed using a two-sample t-test on individual connectivity maps.

5.5 Correlational Analyses with Symptoms

5.5.1 Whole-brain Regression Analyses

The associations between whole-brain reward responsivity and functional connectivity and symptoms were assessed on SPM using one-sample t-tests in the group of interest completed with the symptom severity regressor.

5.5.2 Region of Interest Correlation Analyses

The associations between symptoms and ROI reward responsivity, activity and functional connectivity were assessed on R using ROI-specific extracted beta values and symptom severity scores.

5.6 Stability Analyses

Behavioral and clinical *stability across sites* was calculated as two-sample t-tests on R comparing values from both sites. Assessments of fMRI stability across sites was done on R in mixed models on ROI responsivity betas by adding the variable Site to the between-subject factors.

Behavioral, clinical and fMRI *stability over time* was assessed on R using Intra-Class Correlations (ICC) for SZ and HC scores separately. As a reminder, ICC is a calculation of the ratio between the variance of interest over the total variance of a sample (Fisher, 1992), which has been adapted to assess test-retest reliability in clinical research (Bartko, 1966). ICC calculations give values between 0 and 1. A significant ICC establishes test-retest reliability. Values under .50 indicate poor reliability, values up to .75 indicate moderate reliability, values up to .90 indicate good reliability, and values over .90 indicate excellent reliability.

5.7 Note on Terminology

In contrast to the terminology used in our papers and in the literature, note that *activity* will here refer solely to results based on single regressors (e.g., activity in the No Reward condition), whereas *reward responsivity* will refer to results based on the [High Reward > No Reward] contrast. This distinction is necessary, since the [High Reward > No Reward] contrast does not assess activity per se, but an increase of activity due to the presence of a higher reward.

6. Brief Summary of the Results

6.1 ANTHEA (Acronym for reward ANTicipation in HEAlth)

Carruzzo, F., Giarratana, A., del Puppo, L., Kaiser, S., Tobler, P. N., Kaliuzhna, M. (2023). Neural bases of reward anticipation in healthy individuals with low, mid, and high levels of schizotypy. Scientific Reports, 13, 9953. doi: 10.1038/s41598-023-37103-2

In this paper, we intended to replicate previous results on reward responsivity in healthy controls and to characterize healthy cortico-striatal networks activated during reward anticipation (Research Question 1). To do so, we analyzed MID fMRI data of 84 healthy individuals acquired at the University of Zürich by the laboratory of Prof. Tobler. Behaviorally, we showed that participants responded faster to high reward trials than to no reward trials. Results revealed reward responsivity in the ventral striatum, dorsal striatum, anterior insula, anterior cingulate cortex, ventral tegmental area, thalamus, precuneus, precentral gyrus, dorsolateral prefrontal cortex, inferior parietal gyrus and cerebellum (Figure 12). Results also pointed towards functional connectivity patterns during reward anticipation between the left ventral striatum and the precuneus, anterior insula, precentral gyrus, right dorsal anterior cingulate cortex, mid frontal gyrus, caudate nucleus, inferior operculum and supramarginal gyrus, and the left mid occipital gyrus (Figure 12). We also found functional connectivity between the right ventral striatum and the bilateral precentral gyrus, the right putamen/anterior insula, calcarine gyrus, supplementary motor area and inferior operculum, and the left mid occipital gyrus, superior frontal gyrus and mid frontal gyrus (Figure 13).

We also aimed to evaluate reward responsivity and functional connectivity deficits in schizotypy (Research Question 2). Using SPQ scores, we create three groups: a group of 29 participants with low scores, a group of 24 participants with median scores, and one group of 31 participants with high scores. Our analyses solely focused on the differences between the low SPQ score and the high SPQ score groups. We found no reward responsivity or connectivity difference between the two groups. Additionally, we found no link between reward responsivity and functional connectivity during reward anticipation and SPQ scores or SNS scores.

CRediT Author Statement: Conceptualization (i.e. definition of the scope of the paper), Software (i.e. programming of the MID task using Psychtoolbox on Matlab), Formal Analyses (i.e.

demographic, clinical, behavioral analyses on R and fMRI data analyses using Matlab/SPM12), Writing – Original Draft, Visualization.

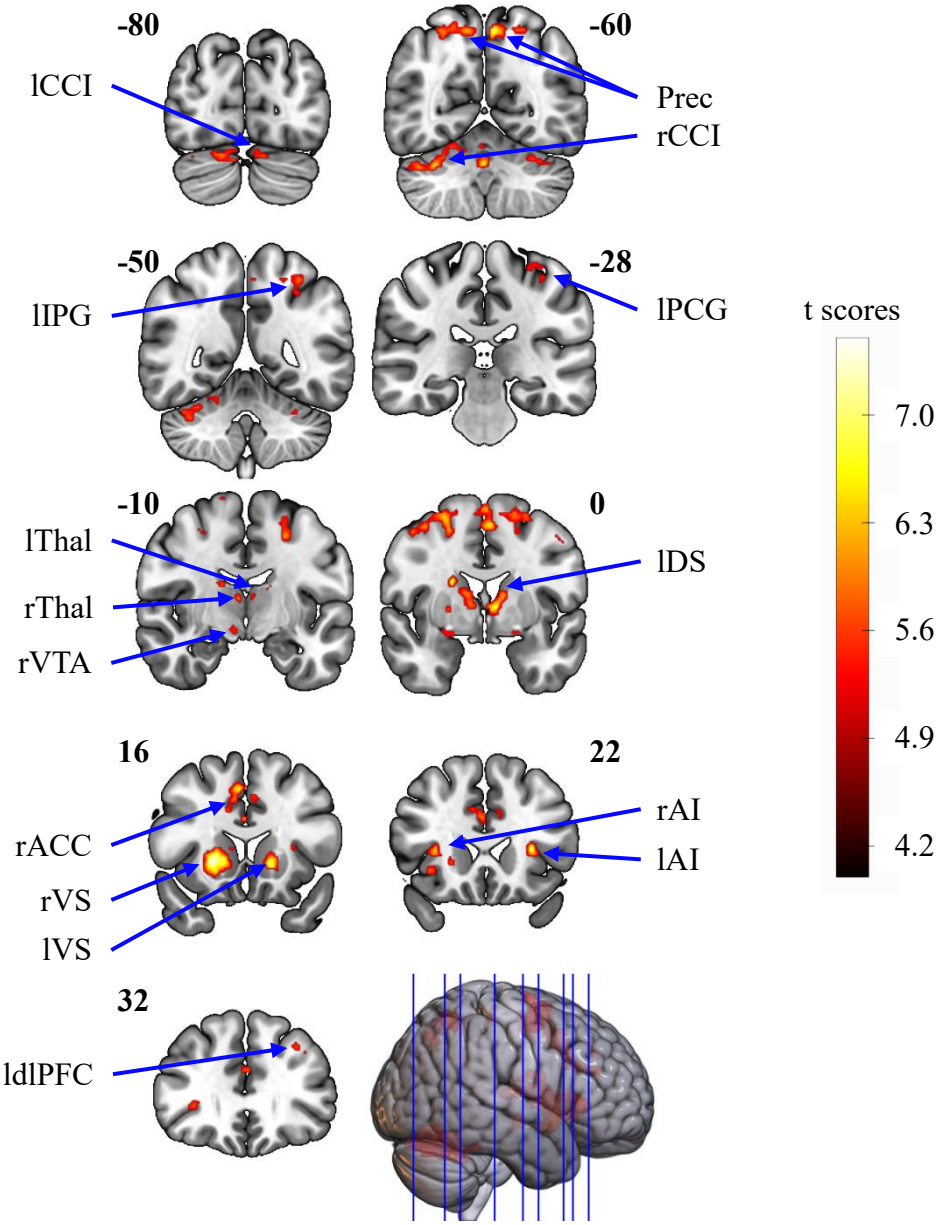

Figure 12. Whole-brain activity analyses (primary threshold of p < .05 FWE, and a cluster-level threshold of p < .05 FWE) showed activations in the bilateral ventral striatum (VS), dorsal striatum (DS), anterior insula (AI), thalamus (Thal), precuneus (Prec) and cerebellum Crus I (CCI); the right anterior cingulum (ACC), ventral tegmental area (VTA); and the left precentral gyrus (PCG), dorsolateral prefrontal cortex (dlPFC) and inferior parietal gyrus (IPG). y coordinates are indicated in bold. Labelling in this and other figures was done using the Automated Anatomical Labelling Atlas 3 (Rolls, Huang, Lin, Feng, & Joliot, 2020).

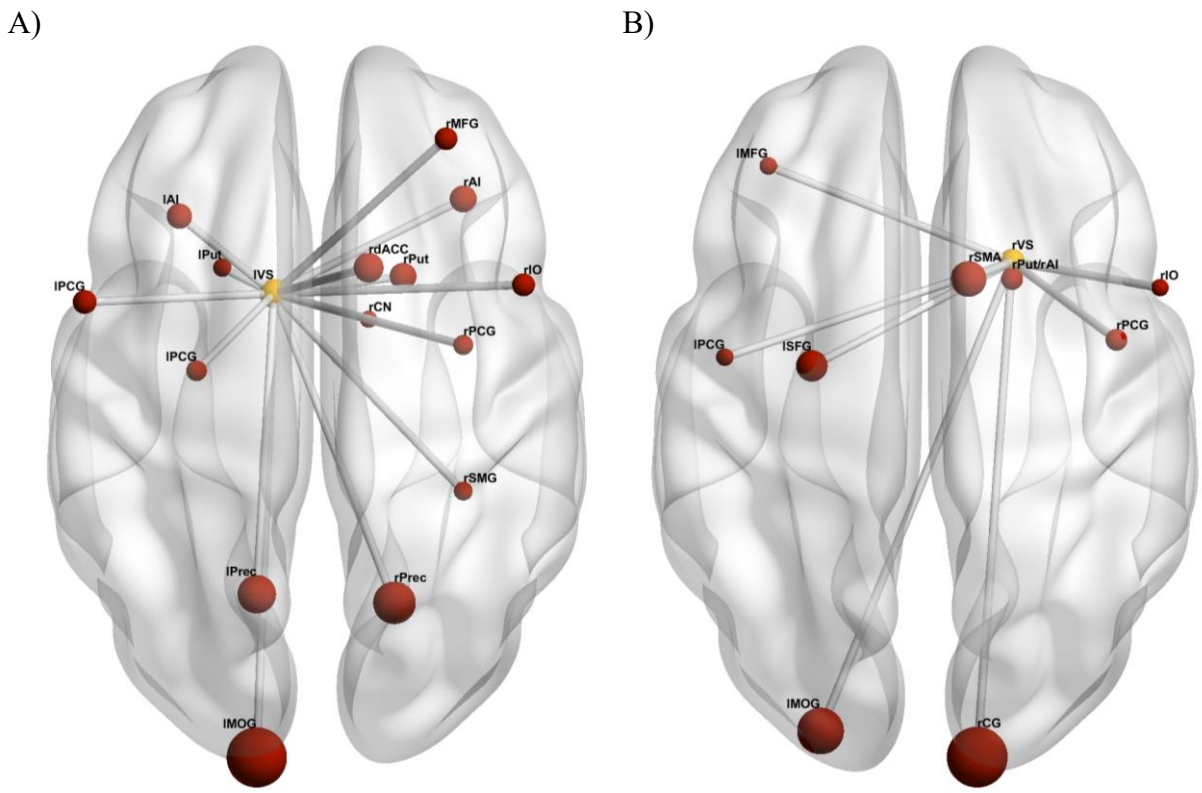

Figure 13. Psychophysiological interaction results (primary threshold of $p < .01$ uncorrected, and a cluster-level threshold of $p < .05$ FWE) for the anticipation phase of the MID task. Whole-brain analysis showed connectivity between the left ventral striatum (lVS) and the bilateral precuneus (Prec), putamen (Put), anterior insula (AI) and precentral gyrus (PCG), the right dorsal anterior cingulate cortex (dACC), mid frontal gyrus (MFG), caudate nucleus (CN), inferior operculum (IO) and supramarginal gyrus (SMG), and the left mid occipital gyrus (MOG). We also found functional connectivity between the right ventral striatum (rVS) and the bilateral precentral gyrus, the right putamen/anterior insula (Put/IA), calcarine gyrus (CG), supplementary motor area (SMA) and inferior operculum, and the left mid occipital gyrus, superior frontal gyrus (SFG) and mid frontal gyrus (MFG). Sphere sizes are based on cluster sizes. Glass brains in this figure were created using BrainNet (Xia, Wang, & He, 2013).

6.2 SYMONE (Acronym for MOtivational NEgative SYmptoms)

Carruzzo, F., Kaliuzhna, M., Kuenzi, N., Geffen, T., Katthagen, T., Schlagenhauf, F., Kaiser, S. (2023). Ventral Striatal Activity during Reward Anticipation as a Neural Marker of Schizophrenia . [Manuscript in preparation for submission to Schizophrenia Bulletin].

In this paper, we sought first to replicate previous results on reward anticipation in schizophrenia using a greater sample. We also aimed to investigate the stability of these results across sites and over time (Research Question 3). To do so, our laboratory collaborated with the laboratory of Prof. Schlagenhauf at Charité University Hospital in Berlin. Together, we set up a set of interviews and experiments to acquire demographic, clinical, cognitive, behavioral and imaging data on a large set of patients with schizophrenia and healthy controls at two different time points. In total, 67 patients with schizophrenia and 55 healthy controls performed the MID. Amongst these participants, 28 patients and 29 controls were recruited in Germany and 39 patients and 26 controls were recruited in Switzerland. Only participants who performed Session 1 and came back three months later for Session 2 were included in our analyses.

Results replicated the higher response time (Figure 14) and the decreased reward responsivity of the left and right ventral striatum in patients with schizophrenia during reward anticipation (Figure 15). Additionally, we showed that negative symptom severity was stable across sites and showed good reliability over the course of three months. Our analyses also indicated that ventral striatal reward responsivity was stable across sites, but showed poor reliability in patients with schizophrenia and moderate reliability in healthy controls. Ventral striatal responsivity correlated with response time speeding in both healthy controls and patients with schizophrenia. In addition, decreased reward responsivity during reward anticipation was also present in the dorsal striatum and in the posterior putamen, and could extend to the anterior cingulate cortex, thalamus and amygdala. Dorsal striatal responsivity also correlated with response time speeding in both healthy controls and patients with schizophrenia. Contrary to previous research, we found no association between ventral striatal reward responsivity in patients with schizophrenia and apathy scores, nor with any other clinical or cognitive measure.

CRediT Authorship Contribution Statement: Conceptualization (i.e. definition of the scope of the paper; designing of the study procedure in inter-lab meeting with our sister laboratory in

Germany), Methodology (refining of MID procedure to allow for testing across two sites; adaptation of the procedure to fit the pandemic context, including the introduction of new safety measures and variable intra-individual delays between sessions), Software (i.e. programming of online questionnaires on RedCap; programming of the MID task using Psychtoolbox on Matlab; programming of streamlined Matlab/SPM12 scripts for fMRI data analysis; implementation of fMRIprep procedure for fMRI data preprocessing, programming of a master script on R to pool demographic, clinical, behavioral and cognitive data from Germany and Switzerland for analysis and storage), Validation (i.e. supervision of the integrability of RedCap data from Germany and Switzerland during questionnaire creation and during data pooling on R), Formal Analyses (i.e. demographic, clinical, behavioral analyses on R and fMRI data analyses using fMRIprep and Matlab/SPM12), Investigation (i.e. screening with psychiatrists of the University Hospital of Geneva (HUG) of over 100 patients with schizophrenia; inclusion and conduction of clinical interviews, cognitive assessment, behavioral tasks and fMRI tasks of 28 patients with schizophrenia and 20 healthy controls; operation of the MRI), Data Curation (i.e. implementation of BIDS format in fMRI data for reproducible research), Writing – Original Draft, Visualization.

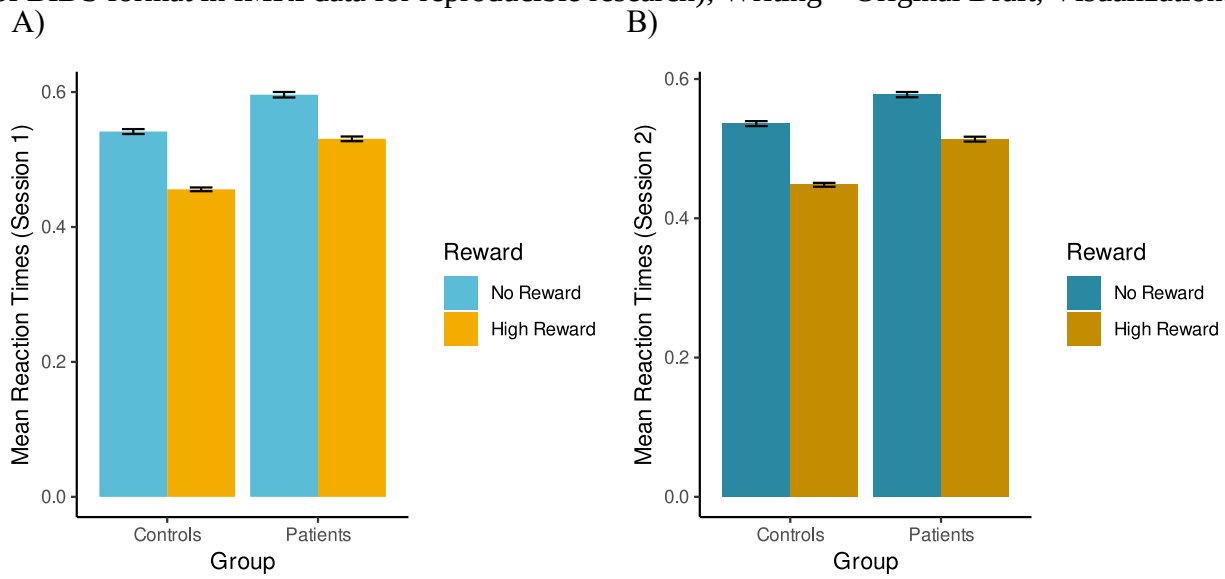

Figure 14. A) Mean response times of high and no reward trials in patients with schizophrenia versus healthy controls in Session 1. B) Mean response times of high and no reward trials in patients with schizophrenia versus healthy controls in Session 2.

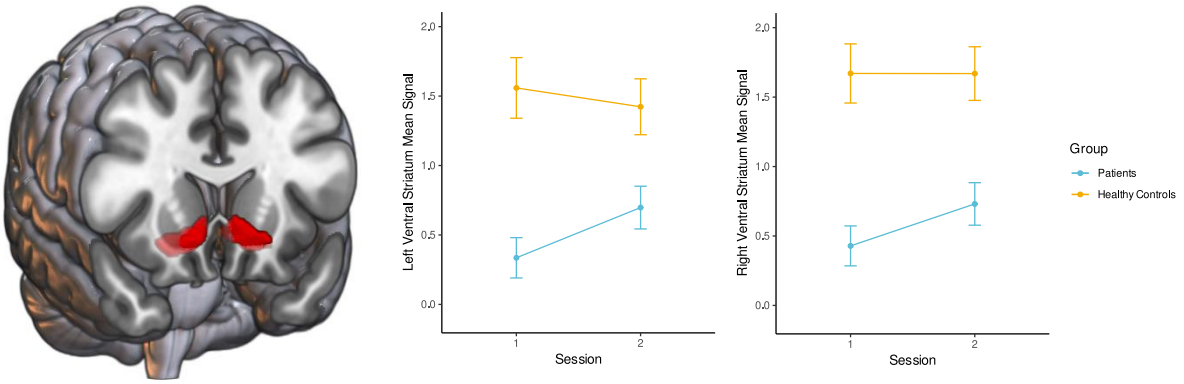

Figure 15. Main effect of Group in Ventral Striatal Mean Signal showing greater activity in Healthy Controls compared to Patients with Schizophrenia. A trending interaction effect shows that Patients with Schizophrenia have more activity in Session 2 than Session 1.

6.3 CORA (Acronym for functional COnnectivity during Reward Anticipation)

Carruzzo, F., Kaiser, S., Tobler, P. N., Kirschner, M., & Simon, J. J. (2022). Increased ventral striatal functional connectivity in patients with schizophrenia during reward anticipation. NeuroImage: Clinical, 33, 102944. doi: 10.1016/j.nicl.2022.102944

In this paper, we aimed to reproduce previous results on ventral striatal reward responsivity. We also intended to explore functional dysconnectivity in patients with schizophrenia and the association between dysconnectivity and apathy (Research Question 3). To do so, we investigated the reward responsivity and cortico-striatal functional connectivity during reward anticipation in 33 healthy controls and 40 patients with schizophrenia. We analyzed MID fMRI data acquired at the University of Zürich during two different studies, both performed in the laboratory of Prof. Kaiser (Kirschner, Hager, Bischof, et al., 2016; Stepien et al., 2018). In this sample, patients with schizophrenia did not show the usual decreased ventral striatal reward responsivity compared to healthy controls. However, their ventral striatal reward responsivity specifically correlated with apathy symptoms.

Our psychophysiological interaction analyses indicated that patients with schizophrenia showed increased functional connectivity between the ventral striatum and the left precuneus and the right parahippocampal gyrus, two nodes of the default mode network (Figure 16). This aberrant connectivity could reflect a compensatory mechanism regulating the activity of the ventral striatum in our sample. We also found that apathy scores correlated negatively with functional connectivity between the left ventral striatum and the left ventral anterior insula / putamen, a region of the salience network, and left dorsal anterior insula / inferior frontal gyrus, regions dedicated to cognitive processes (Figure 17). These networks could represent treatment targets to regulate ventral striatal activity in patients with high apathy.

CRediT Authorship Contribution Statement: Conceptualization (i.e. definition of the scope of the paper), Formal Analyses (i.e. demographic, clinical, behavioral analyses on R and fMRI data analyses using Matlab/SPM8), Writing – Original Draft, Visualization.

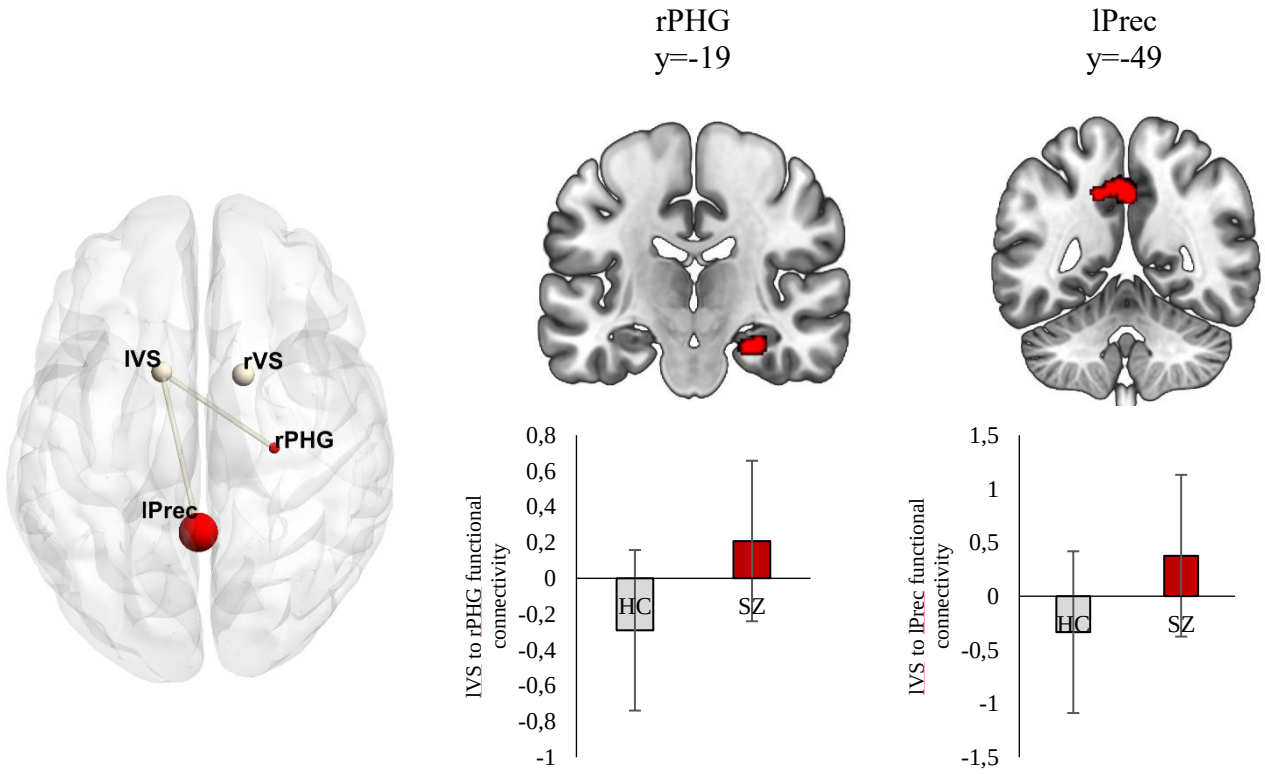

Figure 16. Psychophysiological interaction results for the anticipation phase of the MID task. Whole-brain analyses showed higher connectivity between the left Ventral Striatum (lVS) and the right Parahippocampal Gyrus (rPHG) and the left Precuneus (lPrec) for the Schizophrenia versus Healthy Controls contrast [SZ > HC].

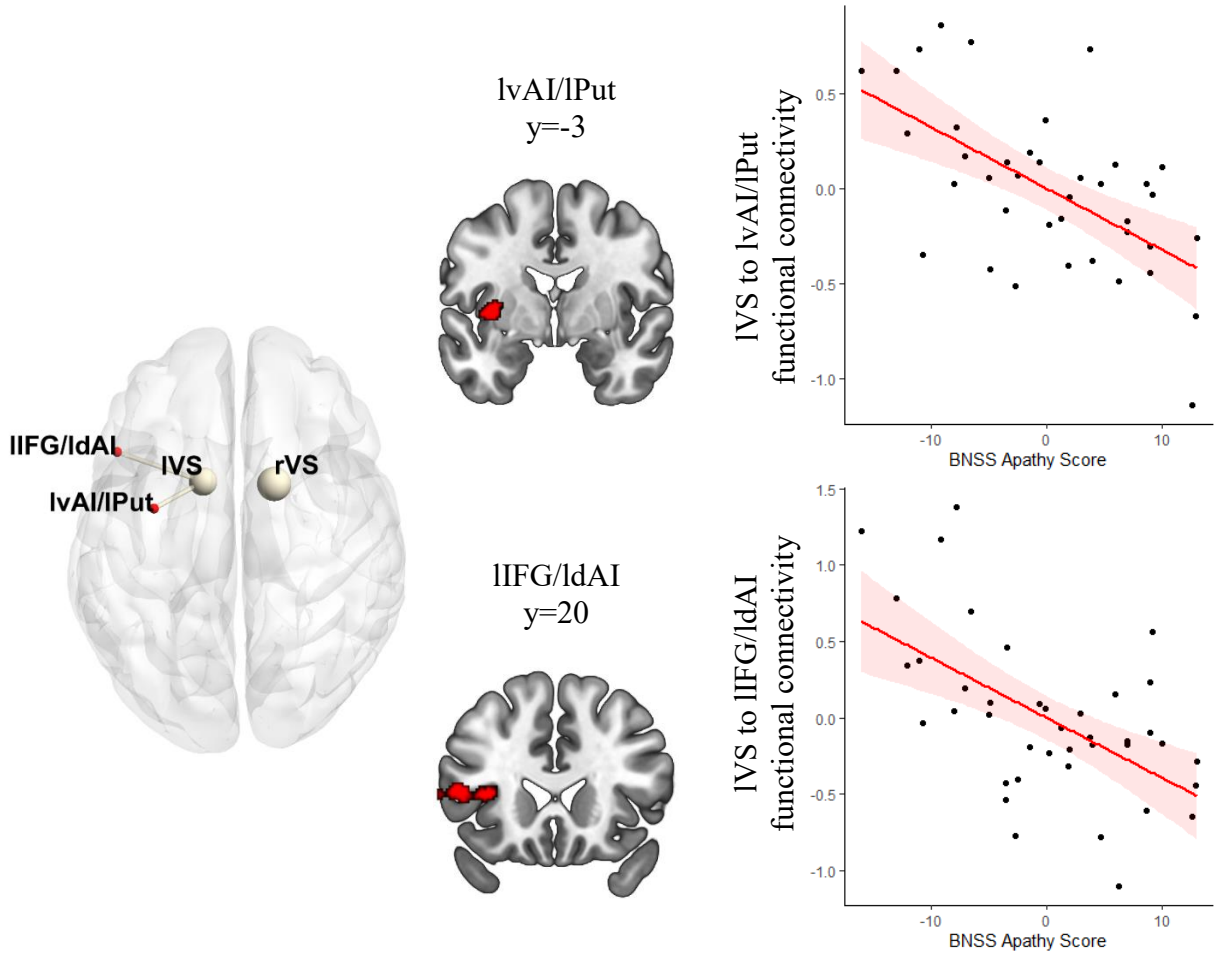

Figure 17. Covariate analysis results for the anticipation phase of the MID task. Negative association between the left Ventral Striatum (lVS) to left ventral anterior insula / left putamen (lvAI/lPut) and left inferior frontal gyrus / left dorsal anterior insula (lIFG/ldAI) connectivity and the apathy score on the Brief Negative Symptom Scale (BNSS), using CPZ equivalence dose as a covariate of no interest. The plots on the right side of the figure are illustrations, plotting residuals of apathy scores and functional connectivity mean beta weights from correlation analyses where the influence of CPZ equivalence dose has been taken out.

7. Discussion

This thesis aimed to expand the knowledge on the neural foundations of reward anticipation functions and dysfunctions in the psychosis continuum. We will therefore discuss our results according to the stages of the psychosis continuum. We will first describe the neural correlates of reward anticipation in healthy individuals. Then, we will explore if reward anticipation is affected in schizotypy. Finally, we will discuss the reproducibility of previous research on reward anticipation in schizophrenia and we will explore new functional connectivity analyses to further define these deficits.

7.1 Reward Anticipation in Health

To characterize and explain reward anticipation deficits, one must first understand what healthy reward anticipation looks like. Our analyses on reward anticipation in 84 healthy individuals in ANTHEA allowed us to 1) replicate previous results on reward responsivity evoked by reward anticipation and 2) explore for the first time in a large cohort of healthy participants cortico-striatal networks that are functionally connected during reward anticipation. These results were then complemented by analyses performed on 55 healthy participants in SYMONE.

7.1.1 Reward Responsivity

Our analyses from ANTHEA found reward responsivity in regions described by Knutson et al. (2000) in their seminal paper on the MID as a tool to analyze reward anticipation. These results have since then been replicated in several meta-analyses on healthy participants (Oldham et al., 2018; Wilson et al., 2018). We first confirmed the importance of the ventral striatum to process reward anticipation. The ventral striatum is thought to process the value of future actions and stimuli by receiving phasic dopamine transients from the mesencephalon (Filimon et al., 2020; Knutson et al., 2000; Williams et al., 2021). It then feeds that information back to the mesencephalon to compute reward prediction error. Accordingly, we found that the ventral tegmental region, a dopaminergic hub of the mesencephalon highly connected with the striatum (Trutti, Mulder, Hommel, & Forstmann, 2019; Yang et al., 2018) also showed higher reward responsivity during reward anticipation. This responsivity could reflect the integration of motivational information when facing highly rewarded trials.

Additionally, processing the value of future actions or stimuli in the ventral striatum is thought to give rise to motivational salience. This salience is then forwarded to neighboring regions to bias cognitive processes towards said actions or stimuli. Accordingly, we found increased reward responsivity in the dorsal putamen, the anterior cingulate cortex and the anterior insula during reward anticipation. The dorsal striatum, connected to motor networks, is thought to integrate ventral striatal information to optimize action selection (Balleine et al., 2007; Oldham et al., 2018). The anterior cingulate cortex and the anterior insula, on the other hand, are part of the salience network (Seeley et al., 2007; Uddin, 2015) and are thought to use motivational salience to bias attentional processes towards actions or stimuli anticipated as rewarding (Rothkirch et al., 2014; Schneider et al., 2018).

The behavioral analyses in ANTHEA and SYMONE concur with this theory. We showed in both studies that healthy controls respond faster to targets associated with higher rewards than targets with no reward. In addition, we showed in SYMONE that ventral striatal reward responsivity during reward anticipation correlates with response time speeding. These results suggest that stimuli or actions with higher motivational salience (as assessed by higher ventral striatal reward responsivity) are processed faster than those associated with a low motivational salience. We also showed that this speeding may be due to better motor preparation. Accordingly, we showed that higher dorsal striatal reward responsivity during reward anticipation leads to increased response time speeding. Indications of greater motor preparation could also be found in ANTHEA, where several regions of the motor networks showed higher reward responsivity when anticipating rewarded stimuli. These regions included the primary motor cortex, supplementary motor area, thalamus and cerebellum. These regions have been shown to participate in reward anticipation in healthy controls (Wilson et al., 2018).

Importantly, analyses in SYMONE confirmed that the ventral striatum is a prime region of interest in studying motivational salience within reward anticipation. Accordingly, we showed for the first time that ventral striatal reward responsivity in healthy controls is stable over a three-month period of time and across two different sites. In addition, our results from ANTHEA and SYMONE also showed that future studies investigating reward anticipation should also focus on the dorsal striatum as a region of interest, as it shows similar reward responsivity, correlations and stability.

In summary, these results show that reward anticipation can modulate goal-directed actions through three different (and possibly co-occurring) processes. First, motivational salience is computed within the ventral striatum and attributed to future actions or stimuli. Second, attentional processes are biased towards rewarded stimuli by activating the salience network. Third, motor preparation for rewarded stimuli is optimized through the recruitment of regions of motor networks, including the dorsal striatum. Based on our results, further analyses should investigate if anterior cingulate cortex and anterior insula reward responsivity also correlate with response time speeding to illustrate better their role in the modulation of attention through motivational salience.

7.1.2 Functional Connectivity

Further implications of the collaboration of these networks to give rise to reward anticipation come from our functional connectivity analyses in ANTHEA. In this study, we explored the regions working together with the ventral striatum during reward anticipation in healthy individuals. However, it is essential to note that functional connectivity analyses do not test causality since they are, in essence, correlational. Thus, we cannot assess the directionality of the connectivity patterns.

As expected, trials associated with a high reward led to functional connectivity between the ventral striatum and regions of the motor network, including the dorsal anterior cingulate cortex and the supplementary motor area. These regions also participate in motor preparation (Asemi, Ramaseshan, Burgess, Diwadkar, & Bressler, 2015). Additionally, our results uncovered functional connectivity between the ventral striatum and the anterior insula, showing the interplay of motivational salience within the salience network to bias attention. The role of the salience network is further corroborated by functional connectivity between the ventral striatum and regions of the attention network, namely the inferior frontal cortex and the supramarginal gyrus, and with regions involved in vision, including the calcarine sulcus and the mid occipital gyrus. Similar to the interaction between motivational salience and motor processes, these functional connectivity patterns can be interpreted as motivational salience working together with visual and attentional preparation to optimize future goal-directed actions.

In summary, our results show that cortico-striatal networks involved in reward anticipation span multiple cortical areas relating to motivational salience, motor, attentional and visual processes.

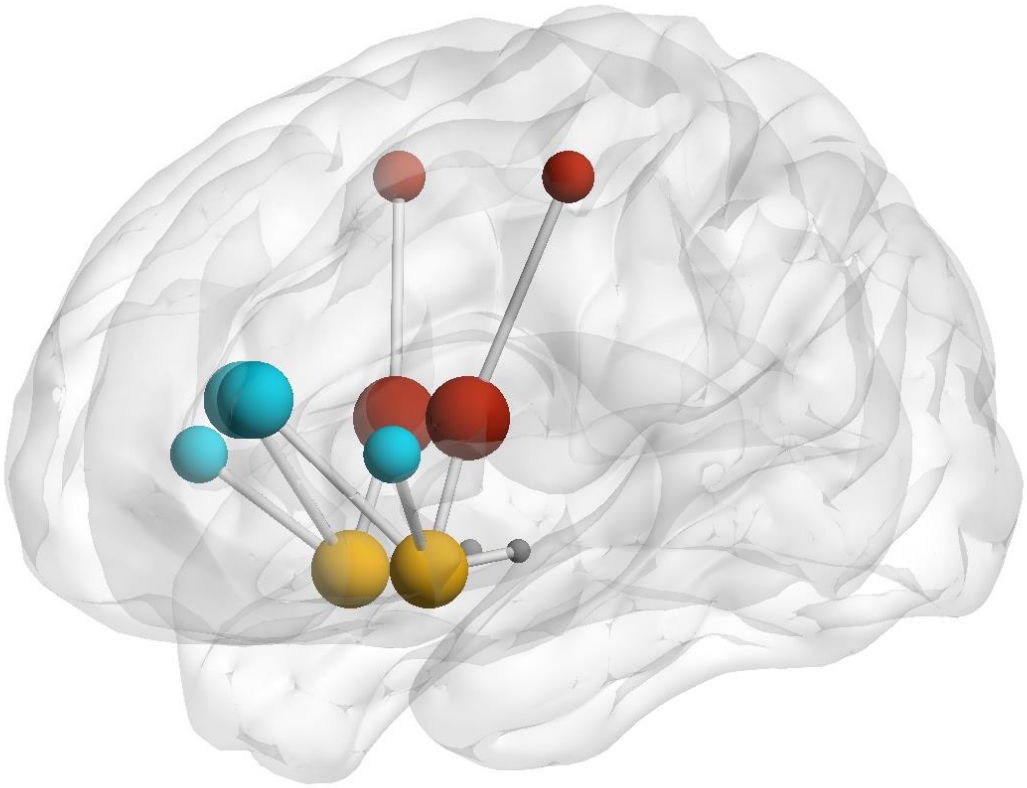

Figure 18. Visualization of the bilateral networks at play during reward anticipation. The ventral striatum (yellow) feeds motivational salience to the salience network (blue) comprising the anterior cingulate cortex and the anterior insula to bias attentional processes towards rewarded options. The ventral striatum also feeds motivational salience to the dorsal striatum and motor cortex (red) to increase motor preparation. The ventral striatum also feeds information back to the ventral tegmental area (grey).

These processes work conjointly to modulate goal-directed behaviors towards rewarded actions or stimuli. Further analyses are necessary to better characterize these networks, notably through correlations with behavioral variables from the MID. Dynamical causal modelling analyses as a method for analyzing directional connectivity would also help to disentangle how these regions influence each other to process reward anticipation.

7.1.3 Preliminary Conclusions

Through these analyses, we could define the neural bases of reward anticipation in healthy controls. Accordingly, we replicated previous results on activation analyses, showing reward

responsivity in the ventral and dorsal striatum, as well as in motor and salience regions. We also defined the implication of the ventral striatum in functional networks taking part in motivation, motor, attentional and visual processes during reward anticipation (Figure 18). Bringing these results together, we strengthened the hypothesis that the ventral striatum gives rise to motivational salience, which works with motor and attentional processes to bias goal-directed actions towards rewarded stimuli.

7.2 Reward Anticipation in Schizotypy

Participants from ANTHEA were screened from the general population based on their Schizotypal Personality Questionnaire (SPQ) scores. Two groups of participants were defined: one group of 29 participants with low scores on the SPQ and one group of 31 participants with high SPQ scores. By comparing the group with high scores to the group with low scores, these analyses allowed us to investigate if reward anticipation deficits are present in schizotypy and, in the presence of deficits, to define their behavioral and neural underpinnings. Since schizotypy is described through similar concepts than schizophrenia (i.e. the SPQ assesses positive, negative and disorganized symptoms), and that patients with schizophrenia show decreased ventral striatal reward responsivity and patterns of dysconnectivity during reward anticipation, we expected individuals with high schizotypy to show comparable neural deficits to those of patients with schizophrenia, though less pronounced.

7.2.1 Clinical Analyses

Our results indicate that healthy individuals with high schizotypy are clinically different from individuals with low schizotypy. Participants with high SPQ scores showed higher levels of both positive and negative symptoms as assessed by the SPQ and SNS.

7.2.1 Reward Responsivity

Contrary to our hypotheses, participants with high schizotypy do not show any sign of reward anticipation deficit. Our analyses from ANTHEA showed no difference in reward responsivity between participants with low SPQ scores and high SPQ scores. Both whole-brain and ventral striatal regions of interest analyses showed similar reward responsivity levels. Accordingly, the two groups performed with similar response times and showed response time speeding in rewarded trials. These results build on evidence that ventral striatal reward responsivity is

preserved in healthy individuals with high schizotypy scores (Kirschner, Hager, Muff, et al., 2016; Yan et al., 2016). In addition, we did not find any relation between ventral striatal reward responsivity and negative symptoms, nor with symptoms in general. These results indicate that, in schizotypy, symptoms may not be due to deficits in regions coding for reward anticipation or that compensatory mechanisms are strong enough to hide that relationship.

7.2.2 Functional Connectivity

Following the results on reward responsivity, our analyses in ANTHEA showed no difference in functional connectivity between participants with high SPQ scores and participants with low SPQ scores and no association between functional connectivity and negative symptoms nor with symptoms in general. These results diverge from previous resting-state studies showing cortico-striatal dysconnectivity in schizotypy (Kozhuharova et al., 2021; Wang et al., 2021). Our results therefore indicate that schizotypal positive and negative symptoms do not arise from dysconnectivities implicated in reward anticipation.

7.2.3 Preliminary Conclusions

Based on our work on healthy participants, we can therefore say that the processes underlying reward anticipation, including motivational salience, motor preparation and attentional biasing, are not affected in schizotypy. Additionally, our results showed that schizotypal positive and negative symptoms are unrelated to reward anticipation deficits. However, we cannot exclude the possibility that individuals with schizotypy experience mild deficits in reward anticipation but are effectively compensated. One strong limitation concerning this study was that our participants comprised mostly young adults, which does not reflect the general population of people showing high schizotypy. Future analyses should include older participants to help strengthen our results.

7.3 Reward Anticipation in Schizophrenia

Compared to schizotypy, reward anticipation deficits in schizophrenia have been thoroughly investigated in the past 20 years. Decreased reward responsivity in the ventral striatum has been repeatedly brought forward as a neural marker of schizophrenia (Leroy et al., 2020; Radua et al., 2015; Zeng et al., 2022). Associations between ventral striatal reward responsivity and negative symptoms, and the apathy dimension in particular, have also been shown in the past (Dowd &

Barch, 2010; Kirschner, Hager, Bischof, et al., 2016; e.g., Radua et al., 2015), though there has been variability in the results. Our analyses comparing 67 patients with schizophrenia and 55 healthy controls in SYMONE allowed us to 1) replicate previous results on reward responsivity and 2) assess the stability of these results over time and across sites. Our analyses in CORA, comparing 33 healthy controls and 40 patients with schizophrenia, 1) offered differing results on reward responsivity and 2) expanded on previous knowledge by assessing functional dysconnectivity during reward anticipation.

7.3.1 Reward Responsivity

Localized analyses in SYMONE again showed the importance of ventral striatal deficiencies during reward anticipation in schizophrenia. Accordingly, we showed a substantial decrease in bilateral ventral striatal reward responsivity during reward anticipation in patients compared to healthy controls. These results concurred with previous meta-analyses (Leroy et al., 2020; Radua et al., 2015; Zeng et al., 2022). We also showed that patients with schizophrenia show reduced response time speeding compared to healthy controls and that patients' response time speeding correlated with their ventral striatal reward responsivity. These results indicate that reward responsivity deficits in schizophrenia lead to the disruption of the processes where motivational salience bias goal-directed behaviors towards rewarded stimuli.

However, analyses from SYMONE also showed that ventral striatal reward responsivity in patients with schizophrenia did not correlate with apathy, nor with negative symptoms in general. These results go against previous research which found such an association (e.g., Kirschner, Hager, Bischof, et al., 2016; Radua et al., 2015; Stepien et al., 2018). Conversely, analyses from CORA, which followed the same procedure as SYMONE, did not find a decrease in ventral striatal reward responsivity in patients with schizophrenia but still showed a correlation between ventral striatal reward responsivity and apathy. This double dissociation of results made us consider several factors that could explain such discrepancies.

First, schizophrenia is a heterogeneous disorder, and pools of patients often show high variability in symptom severity, education, disease duration and medication, amongst others. Studies with limited numbers of participants could therefore lack sufficient power to produce robust results. In the case of CORA, sampling participants from two pools of participants further adds to this issue. The pools of patients with schizophrenia from SYMONE and CORA also differed on

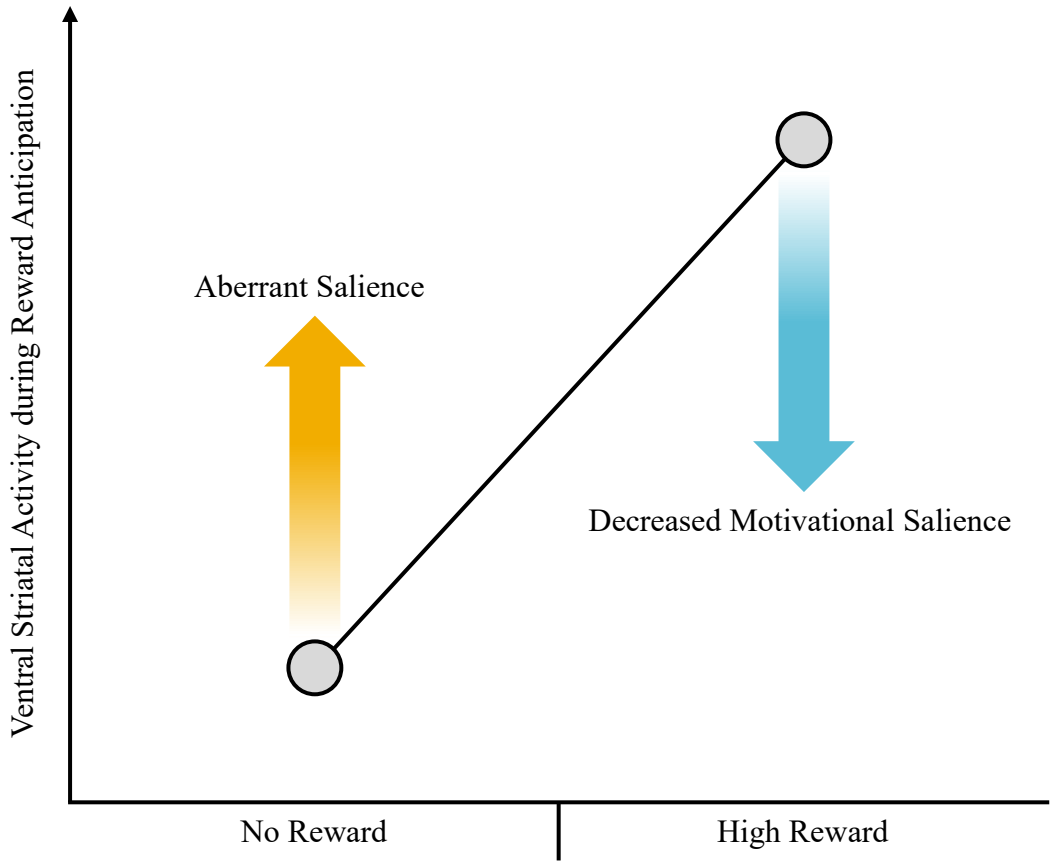

Figure 19. Ventral striatal activity during the Monetary Incentive Delay (MID) task. Two processes can lead to decreased ventral striatal activity during reward anticipation: abherrant salience at rest, visible as increased activity in the no reward condition and decreased motivational salience, represented as decreased activity in the high reward condition.

medication and age, with patients from CORA being younger ($diff_{age}$ = -6.15, t = -3.30, p < .01) and receiving a higher antipsychotic dose ($diff_{ris\_equivalence}$ = 2.69, t = 3.06, p < .01) than patients in SYMONE. Inclusion criteria can also differ between studies. For example, patients from CORA were recruited in out-patient and in-patient units, whereas patients from SYMONE were exclusively recruited from out-patient units.

Second, the interpretation of decreased reward responsivity during reward anticipation compared to healthy controls can be misleading. As a reminder, reward anticipation is calculated as the contrast between high reward trials and no reward trials. Therefore, the level of activity for no reward trials is removed from the results. In healthy participants, the interpretation is

straightforward: the no reward condition represents baseline activity, and the contrast between high and no reward trials leads to a positive value, meaning that there is more activity in high reward trials compared to no reward trials. It is then easy to assume that decreased reward responsivity during reward anticipation in patients with schizophrenia is due to decreased activity for high reward trials specifically. Nevertheless, decreased reward responsivity can also be due to higher activity for no reward trials or a combination of higher activity for no reward trials and decreased activity for high reward trials (Figure 19). While these three conditions functionally result in decreased reward responsivity during reward anticipation, the interpretation of that decrease is drastically different depending on the condition.

Accordingly, a specific decrease in high reward trials activity may reflect a decrease in motivational salience. On the other hand, a specific increase in no reward trials activity points toward aberrant salience, which has been put forward as a cause for positive rather than negative symptoms (Kapur, 2003). A deeper look at the analyses from SYMONE and CORA indicates that different processes could be at play between the two studies (Figure 20). While patients from CORA showed regularized activity in all conditions, patients from SYMONE showed increased activity in no reward trials and decreased activity in high reward trials. Note that the results from CORA discussed here have been re-extracted data using the ventral striatal anatomical ROIs from SYMONE to be compared more easily. Interestingly, apathy scores in CORA specifically correlated with decreased activity in high reward trials and not in no reward trials. Such discrepancies could help us understand why ventral striatal reward responsivity is sometimes decreased compared to healthy controls and sometimes not. It also gives hints as to why that responsivity sometimes correlates with positive symptoms and sometimes with negative symptoms. Creating a new MID rest condition unrelated to rewards could help disentangling these processes by allowing us to assess aberrant and motivational salience more specifically.

Should ventral striatal reward responsivity be considered as a neural marker of negative symptoms? Our results show that the relationship between reward responsivity and negative symptoms might be more complicated than previously thought. Then, could ventral striatal reward responsivity be considered as a neural marker of schizophrenia? Our results in SYMONE confirm that reward responsivity deficits are clearly present in patients with schizophrenia and is comparable across sites. However, intra-class correlation analyses showed that the reliability

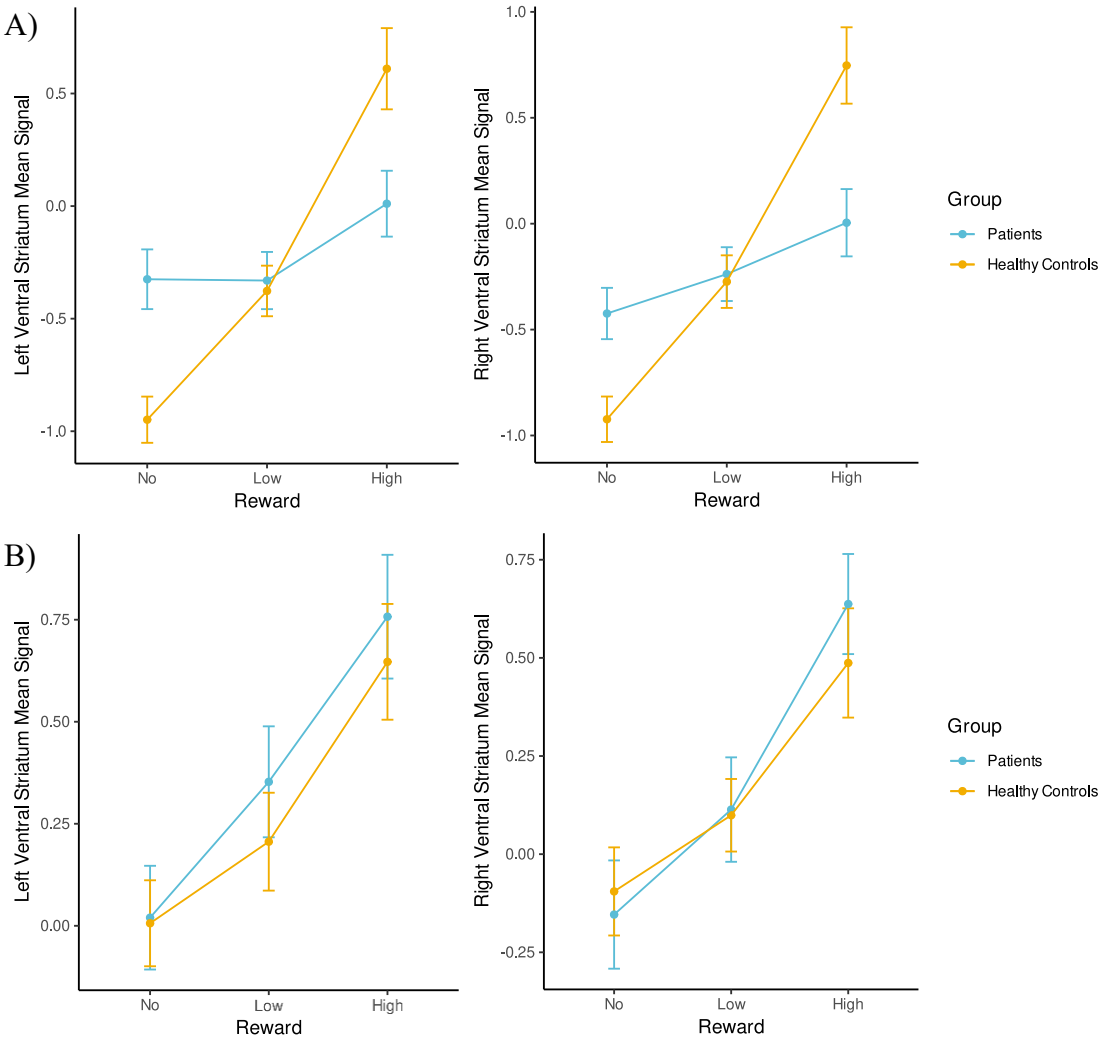

Figure 20. Ventral striatal activity during the Monetary Incentive Delay (MID) task in Healthy Controls and Patients with Schizophrenia from A) SYMONE and B) CORA.

over the course of three months of ventral striatal reward responsivity in patients was poor, and only moderate in healthy controls. Unfortunately, this problem not surprising, as fMRI results are known to have poor reliability (Elliott et al., 2020). Additional analyses are necessary to determine which processes underlying reward responsivity are truly affected in patients with schizophrenia, and if a clear link to these processes could be described.

To further complicate the case, changes in reward responsivity in patients with schizophrenia are not specific to the ventral striatum. Accordingly, our results from SYMONE also pointed towards other regions showing decreased reward responsivity during reward anticipation in

patients with schizophrenia. First, our analyses showed that the dorsal striatum and posterior putamen were affected similarly to the ventral striatum. Accordingly, dorsal striatal reward responsivity in patients with schizophrenia correlated with response time speeding and response time speeding was itself diminished in schizophrenia. Based on previous research and on our results in healthy controls, these results indicate that patients with schizophrenia also show deficits in motor preparation. Additionally, we found decreased reward responsivity in the anterior cingulate cortex, amygdala and calcarine sulcus, indicating that patients with schizophrenia might also have difficulties using motivational salience to bias visual attention towards rewarded trials.

Taken together, these results indicate that several regions known to be responsive to rewards in healthy controls are affected in schizophrenia. These regions are all part of larger networks involved in goal-directed behaviors. Their decreased reward responsivity at least partly explains why patients with schizophrenia benefit less from rewards compared to healthy controls. However, we also showed that traditional reward anticipation analyses could not be specific enough to probe links with symptoms, as they may fail to discriminate different processes at play during reward anticipation. We also showed unsatisfactory results to consider ventral striatal reward responsivity as a neural biomarker of schizophrenia, let alone negative symptoms. A deeper look at the single regressors of the MID could offer more precise measurements of the psychological processes affected in schizophrenia.

7.3.2 Functional Connectivity

Our analyses on cortico-striatal functional connectivity during reward anticipation from CORA unveiled increased functional connectivity between the ventral striatum and regions of the default mode network. These results diverge from one previous task-based study and several resting-state fMRI studies that mainly found decreased functional connectivity in patients with schizophrenia (Fornito et al., 2013; Simon et al., 2015; Tu, Hsieh, Li, Bai, & Su, 2012). However, the patterns of increased connectivity we found might be specific to our sample and could represent a compensatory mechanism. Accordingly, the patients from this sample showed normalized ventral striatal activity during reward anticipation. However, they still showed behavioral signs of difficulties in integrating motivational salience, with less response time speeding for high reward trials compared to healthy controls. An increase in cortico-striatal

connectivity could reflect a neural effort to upregulate ventral striatal activity during reward anticipation and produce motivational salience.

This hypothesis is strengthened by the fact that increased functional connectivity and response time speeding were associated in CORA. In other words, the more functional connectivity they expressed, the better their performance on the MID and, therefore, the better their attribution of motivational salience to high reward trials. Our exploratory analyses on two nodes of the salience network, the anterior cingulate cortex and the anterior insula, also showed increased connectivity with the cortex during reward anticipation. These results add to the hypothesis that salience processing was still disrupted in these participants, despite showing normalized ventral striatal activity.

Furthermore, we uncovered a link between cortico-striatal functional connectivity and apathy symptoms. Patients with higher apathy symptoms also had less functional connectivity between the ventral striatum and the anterior insula. These results complement well previous results that found links between dysconnectivities in schizophrenia and negative symptoms (Brakowski et al., 2020; Shukla et al., 2018; Tian et al., 2019; Wang et al., 2016). Our results indicate that patients with high levels of apathy show difficulties creating motivational salience during reward anticipation and feeding that information to the salience network to optimize goal-directed behaviors. Further analyses of data from SYMONE will give us a better understanding of how generalizable the dysconnectivity we found is, or if patients with impaired ventral striatal reward responsivity show different patterns of dysconnectivity.

7.3.3 Preliminary Conclusions

Our results from SYMONE and CORA replicated previous results showing decreased ventral striatal reward responsivity and specific associations between ventral striatal reward responsivity and apathy. However, we demonstrated that different cohorts of patients with schizophrenia could show significant variability in ventral striatal responsivity depending on the underlying processes at play during reward anticipation. These results could also explain the variability in the studies linking ventral striatal reward responsivity and symptoms in schizophrenia. We showed that participants who experience high levels of apathy associated with decreased ventral striatal reward responsivity also show dysconnectivities within the salience network. Taken

together, these results provide further evidence of a global disruption of the salience network in schizophrenia and its relation to apathy.

7.4. Limitations

Several limitations should be considered regarding the interpretation of our results. First, the three studies presented here are not perfectly comparable. While the MID procedure was closely matched between studies, the MRI machines, sequences and programs used to analyze the data differed. Ventral striatal ROI definition was also different between studies, with functional ROIs favored in ANTHEA and CORA and anatomical ROIs used in SYMONE (though we did re-run analyses from CORA with anatomical ROIs to facilitate comparisons with SYMONE results). This discrepancy introduces unwanted variability in our results.

In addition, despite our best efforts to recruit large cohorts of participant either by pooling studies together, or by recruiting participants from two different sites, our numbers are still moderate. Our results were still associated with large effect sizes, especially in SYMONE. However, new studies based on multi-site databases pooling thousands of participants together could offer better insights on the presence or absence of sub-groups to discriminate the underlying processes of reward anticipation deficits in schizophrenia.

As mentioned earlier, one specific limitation of our ANTHEA study is that participants are all young adults. Our account on healthy reward responsivity and functional connectivity is therefore not perfectly generalizable. Additionally, reward anticipation deficits could be efficiently compensated in young adults, and could appear in older individuals. Therefore, studies on schizotypy including more variability on age are necessary.

This thesis also explored task-based functional connectivity during reward anticipation in three stages of the psychosis continuum. Our results complement well previous research on reward responsivity. They give interesting accounts on the state of cortico-striatal networks during reward anticipation in those stages. However, more functional connectivity research needs to be done to strengthen them.

8. Conclusions

This thesis aimed to assess reward anticipation in health, schizotypy and schizophrenia, three stages of the psychosis continuum. Our reward responsivity and functional connectivity analyses

on healthy controls allowed us to describe the neural underpinnings of reward anticipation. We showed that reward anticipation relies on the ventral striatum working together with regions of the salience, motor and attention networks to optimize goal-directed behaviors. We then showed that schizotypy is not associated with any reward anticipation deficiency, despite the presence of symptoms. We cannot exclude the possibility that mild deficiencies are effectively compensated in these participants. Finally, we confirmed the presence of reward anticipation deficits in schizophrenia. We showed that all the networks defined in healthy controls are affected in schizophrenia, either locally or within functional networks. We also showed that apathy is specifically related to deficits in the salience network in one cohort of patients.

As such, this thesis showed that reward anticipation is differentially affected along the psychosis continuum. Further analyses on intermediate stages of the continuum, like Ultra High Risk and First Episode Psychosis individuals, could help define the disease stage at which reward anticipation deficits appear. On the other hand, traditional reward anticipation analyses might lack specificity to properly assess the neural correlates of positive and negative symptoms on the continuum, as processes linked to positive and negative symptoms could lead to similar reward anticipation deficiencies and might hide such associations.

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Annexes

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