# Pathophysiological changes of neurofunctional interaction between the dopaminergic reward system and the hippocampus in schizophrenia and bipolar disorder

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Sarah Wolter

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**Betreuungsausschuss**

1. Betreuer: Prof. Dr. Oliver Gruber, Sektion für Experimentelle Psychopathologie und Bildgebung, Klinik für Allgemeine Psychiatrie, Universitätsklinikum Heidelberg

2. Betreuer: Prof. Dr. Andreas Glöckner, Allgemeine Psychologie - Urteilen, Entscheiden, Handeln, FernUniversität in Hagen

3. Betreuer: Dr. Igor Kagan, Kognitive Neurowissenschaften, Deutsches Primatenzentrum, Göttingen

**Mitglieder der Prüfungskommission**

Referent: Prof. Dr. Oliver Gruber, Sektion für Experimentelle Psychopathologie und Bildgebung, Klinik für Allgemeine Psychiatrie, Universitätsklinikum Heidelberg

Koreferent: Dr. Igor Kagan, Kognitive Neurowissenschaften, Deutsches Primatenzentrum, Göttingen

**Weitere Mitglieder der Prüfungskommission**

Prof. Dr. Andreas Glöckner, Allgemeine Psychologie - Urteilen, Entscheiden, Handeln, FernUniversität in Hagen

Prof. Dr. Hansjörg Scherberger, Neurobiologie, Deutsches Primatenzentrum, Göttingen

PD Dr. Peter Dechent, MR Forschung in der Neurologie und Psychiatrie, Universitätsmedizin Göttingen

Dr. Roberto Goya-Maldonado, Labor für Systemische Neurowissenschaften und Bildgebung in der Psychiatrie, Klinik für Psychiatrie und Psychotherapie, Universitätsmedizin Göttingen

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# I. Summary

Schizophrenia and bipolar disorder are severe psychiatric disorders with an overlap in both genotype and phenotype (Cosgrove & Suppes, 2013). Moreover, patients of both disorders have previously been reported to display abnormalities within the dopaminergic reward system (Ashok et al., 2017; Howes & Kapur, 2009), although the nature of these abnormalities is not yet well understood. While former versions of the dopamine hypothesis of psychosis assumed the dopaminergic system to be hyperactive in schizophrenia patients (van Rossum, 1966), more recent versions suggest that the dopaminergic system may be normal in its configuration, but abnormally regulated (Grace, 2012). One candidate modulator region, which might be dysfunctional in schizophrenia, is the hippocampus. In animal models of schizophrenia neurons of the anterior hippocampus have been shown to be hyperactivated, leading to a substantially increased number of spontaneously firing dopamine neurons and thereby increasing the amplitude of the phasic response of dopaminergic neurons in response to salient stimuli (Grace, 2012). Although bipolar disorder is characterized by dopaminergic abnormalities as well, findings about these abnormalities are less consistent (Ashok et al., 2017). Furthermore, there are studies showing both structural and functional abnormalities of the hippocampus (Brambilla et al., 2008; Ng et al., 2009; Otten & Meeter, 2015). Nevertheless, animal models of bipolar disorder do not include lesions of the hippocampus.

In the sense of translational research, the goal of this thesis was to investigate the functional interaction of hippocampus and dopaminergic reward system in human patients to confirm and validate findings from animal models in schizophrenia and to inform prospective research with animal models of both schizophrenia and bipolar disorder.

Using fMRI, I examined reward-related brain activation and connectivity of the hippocampus and central regions of the dopaminergic reward system, e. g. ventral tegmental area (VTA) and ventral striatum, in a group of 20 schizophrenia patients (study 1) and in a group of 20 bipolar patients (study 2) compared to healthy controls. Therefore, I adapted a modified version of the desire-reason dilemma (DRD) paradigm for the needs and cognitive capacities of psychiatric patients. In this paradigm context-dependent reward stimuli are presented, which have previously been proven to activate both the dopaminergic system and the hippocampus (unpublished data by our group).

The selection of context-dependent reward stimuli was associated with a coactivation of bilateral hippocampus, VTA and ventral striatum in healthy controls and both schizophrenia

and bipolar patients. Critically, the left ventral striatum activation was abnormally increased in schizophrenia, as previously shown in the study of Richter and colleagues (2015). Furthermore, task-related activity of both the hippocampus and the VTA, was positively correlated with the severity of psychotic symptoms. Although hippocampal structural (e.g. Bogerts et al., 1993; Zierhut et al., 2013) and functional (e.g. Heckers, 2001; Jardri et al., 2011; Lefebvre et al., 2016; Liddle et al., 2000; Schobel et al., 2009) abnormalities have already been noted in previous studies to be related to psychotic symptoms, this is the first neuroimaging study in humans showing both psychosis-related hippocampus activation and psychosis-related activation of the dopaminergic midbrain/VTA, thereby linking hippocampal abnormalities to the hyperdopaminergic state in schizophrenia. As findings from animal models of schizophrenia indicate that VTA activation is dependent on an activation of the hippocampus (for review see e.g. Grace, 2012, 2016), hyperactivation of the hippocampus and the VTA can be expected to be functionally related. In line with that, our study revealed a positive coupling of the left hippocampus with the bilateral VTA in healthy controls. Our results show, that this functional connectivity is disrupted in schizophrenia patients, with a higher psychotic symptom severity related to a reduced functional connectivity. The results of this study are of high relevance, as they shed light on the pathophysiological mechanisms underlying psychotic symptoms in schizophrenia, identifying hyperactivation and dysfunctional coupling of the hippocampus and the VTA as possible neuroimaging markers for psychosis.

Replicating the findings from Trost and colleagues (2014), the vStr showed a reduced reward-related activation in bipolar patients compared to healthy controls. Interestingly, this was accompanied by a reduced functional connectivity between hippocampus and VTA, matching the findings from the schizophrenia patients. Although there is evidence from multiple studies concerning abnormal hippocampal structure and function in bipolar disorder (Brambilla et al., 2008; Ng et al., 2009; Otten & Meeter, 2015), this is the first study showing functional connectivity abnormalities of the hippocampus with the dopaminergic midbrain – thereby revealing a shared pathophysiological mechanism of bipolar disorder and schizophrenia.

# II. List of abbreviations

| | |
|---|---|
| avPFC | anterior ventral prefrontal cortex |
| BD | bipolar disorder |
| BDI | Beck Depression Inventar |
| CGI | Clinical Global Impression Scale |
| DA | dopamine |
| DAT | dopamine transporter |
| DRD | desire-reason dilemma |
| dStr | dorsal striatum |
| fMRI | functional magnetic resonance imaging |
| HPC | hippocampus |
| MAM | methyl azoxymethanol |
| MID | monetary incentive delay |
| MNI | Montreal Neurological Institute |
| NAcc | nucleus accumbens |
| PANSS | Positive and Negative Syndrome Scale |
| PET | positron emission tomography |
| PFC | prefrontal cortex |
| ROI | region of interest |
| SAD | schizoaffective disorder |
| SN | substantia nigra |
| SPECT | single-photon-emission computed tomography |
| SZ | schizophrenia |
| T | Tesla |

| | |
|---|---|
| vStr | ventral striatum |
| VTA | ventral tegmental area |
| WHO | World Health Organization |
| WM | working memory |

# 1 General introduction

## 1.1 Neurofunctional interaction between the dopaminergic reward system and the hippocampus

This chapter is subdivided into three sections. The aim of the first section is to introduce the dopaminergic system, as it seems to be implicated in the pathophysiology of both schizophrenia (SZ) and bipolar disorder (BD) and is therefore of high relevance for the current thesis. For the same reason, the hippocampus (HPC) is decribed in the second section of this chapter. As the hippocampus and the dopaminergic reward system interact with each other and this interaction seems to be relevant for the pathophysiology of SZ and hypothetically also for BD, the third section summarizes the findings about this interaction.

### 1.1.1 Dopaminergic reward system

Dopamine (DA) is a neurotransmitter of the brain, that is mainly synthesized and released in two midbrain areas containing dopaminergic neurons: the ventral tegmental area (VTA) and the substantia nigra (SN) (Bentivoglio et al., 2005). Regarding the origin and target region of the dopaminergic projections, three pathways can be differentiated. The mesolimbic and the mesocortical pathways are dopaminergic projections with an origin in the VTA. The former one is projecting to the ventral striatum (vStr) including the nucleus accumbens (NAcc), whereas the latter one is targeting the prefrontal cortex (PFC). With the origin in the SN the nigrostriatal pathway is projecting to the dorsal striatum (dStr) including putamen and nucleus caudatus (Björklund & Dunnett, 2007).

Five distinct DA receptor types ($D_1$-$D_5$) have been identified. Nevertheless, these five DA receptors can be summarized in two categories: the D1-like receptors (D1, D5) and the D2-like receptors (D2, D3, D4). The most wide-spread DA receptor in the human brain is the D1 receptor. A high DA D1 and D2 receptor density can be found in the striatum (Missale et al., 1998). The striatum is a nucleus in the subcortical basal ganglia of the forebrain. It is divided into ventral and dorsal parts. While the dStr is mainly implicated in motor function, the vStr is mainly involved in reward processing (Haber & Knutson, 2010).

The role of the vStr in reward processing was first described by Olds and Milner (1954). In an electrical self-stimulation study with rats, they could show that stimulation of the vStr – among other regions – was experienced as rewarding – as stimulation of this region was excessively and persistently repeated. Further evidence for this role of the vStr was coming from

pharmacological studies – showing that "amphetamine-stimulated release of DA in nucleus accumbens can increase the incentive value of neutral stimuli with which it is paired" (Carr & White, 1983, p. 2551). Besides, human functional magnetic resonance imaging (fMRI) studies (Aharon et al., 2001; Anderson et al., 2003; Delgado et al., 2000; Diekhof & Gruber, 2010; Elliott et al., 2000; Gottfried et al., 2002; Knutson et al., 2000; Menon & Levitin, 2005; Mobbs et al., 2003; O'Doherty et al., 2001; Rolls et al., 2003) and positron emission tomography (PET) studies (Blood & Zatorre, 2001; Künig et al., 2000; Martin-Sölch et al., 2001; Small et al., 2001) provide more evidence for the relevance of the vStr in reward processing by showing vStr activity in response to primary and secondary rewards. While primary reward stimuli elicit a biological determined response without learning, secondary rewards reinforce a behavior after they have been associated with a primary reward. During this learning process, which uses mechanisms of classical conditioning, NAcc DA release shifts from the unconditioned (primary) reward stimulus to the conditioned (secondary) reward stimulus (Day et al., 2007).

However, it is discussed controversially, which phase of reward processing is related to vStr activation. On the one hand, there are studies showing that only reward anticipation but not consumption is accompanied by vStr activation (Breiter et al., 2001; Knutson et al., 2001b; 2003; O'Doherty et al., 2002), otherwise there are also studies reporting reward-related activity during the consumption phase (Delgado et al., 2003; 2000; Diekhof & Gruber, 2010). The degree of vStr activation seems to vary with the magnitude (Knutson et al., 2001a; Yacubian et al., 2006), uncertainty (Cooper & Knutson, 2008; Dreher et al., 2006; Knutson et al., 2005; Preuschoff et al., 2006), probability (Abler et al., 2006; Hsu et al., 2009; Tobler et al., 2008; Yacubian et al., 2006) and delay (Abler et al., 2006; Hsu et al., 2009; Tobler et al., 2008; Yacubian et al., 2006) of anticipated monetary rewards as well as with the necessary effort to obtain the reward (Croxson et al., 2009). In addition, there are several studies demostrating that vStr activity is also sensitive for reward omissions, in a way that omissions of rewards can lead to decreased vStr activation (Berns et al, 2001). Accordingly, the reward prediction error theory proposes that vStr activation is dependent on the prediction error of reward, which is the difference between expected and obtained rewards (McClure et al., 2007; Montague et al., 1996; Schultz et al., 1997).

Afferent and efferent projections are summarized in review by Haber and Knutson (2010): Besides the previous mentioned dopaminergic projections, the vStr receives also glutamatergic input. Glutamatergic input is coming from the cerebral cortex (particularly limbic areas) and the thalamus. Output from the vStr is mainly sent to the pallidum and midbrain. Further, there

are efferent projections to the pedunculopontine nucleus, lateral hypothalamus, periaqueductal gray, bed nucleus and nucleus basalis in the basal forebrain (Haber & Knutson, 2010).

### 1.1.2 Hippocampus

The HPC is located bilaterally in the medial temporal lobes of the brain and belongs to the limbic system (Berger & Thompson, 1978). The shape of the HPC has been compared to a seahorse and a ram`s horn (Cornu Ammonis) (Witter 2009). The HPC is suggested to have different functions in cognitive processing (see Andersen et al., 2007 for a review): Lesions of the HPC have major impact on cognitive functioning, mainly disrupting memory. The most famous case described in the literature is the patient H.M., who was having profound memory loss following bilateral resection of medial parts of the temporal lobe. Moreover, neurophysiological studies in rodents show that some of the neurons of the HPC serve as "place cells" representing locations in space and therefore creating cognitive maps. Furthermore, the HPC's role in context processing and context-dependent memory has often been reported as well (Acheson et al., 2012; Fanselow, 2000; Jarrard, 1995; Rugg et al., 2012; Sharp, 1999).

Although the HPC is one of the most extensively studied regions of the brain, it is still under debate which anatomical regions belong to the HPC. While some authors include the dentate gyrus and the subiculum (Grace, 2012), others say that these regions among the HPC, the presubiculum, the parasubiculum and the entorhinal cortex form a functional system called the hippocampal formation, whereas the HPC proper is only consisting of CA1, CA2, CA3 and CA4 (CA abbreviates cornu ammonis) (Andersen et al., 2007). In addition, the HPC is subdivided into an anterior and a posterior part (ventral and dorsal part in animals) and sometimes an additional intermediate part is described (Fanselow & Dong, 2010). On the one hand, these subdivisions are based on the differential afferent and efferent connectivity of the anterior and posterior compartments, and on the other hand, they are based on the speculation that the anterior part is more involved in "hot" (limbic) processing, whereas the posterior part is more involved in "cold" processing such as spatial navigation or learned associations (Fanselow & Dong, 2010; Jung et al., 1994; Moser & Moser, 1998; Poppenk et al., 2013; Robinson et al., 2015). Strong support for this functional segregation of the HPC comes from fMRI studies (Duarte et al., 2014; Duncan et al., 2014; Greve et al., 2011; Prince et al., 2005; Strange et al., 2005).

Projections of the hippocampus are widespread, reaching cortical and subcortical areas of the brain, and differ between the substructures. Except for small differences, anatomy and structural connectivity of the HPC seem to be very similar in animals (e.g. rodents, non-human primates)

and humans (Andersen et al., 2007). However, trans-species functional commonalities and differences remain to be elucidated.

As the ventral HPC connection with the NAcc and its role in reward processing is of particular interest for the present thesis, this interaction is further described in the following section.

### 1.1.3 Interaction of the dopaminergic reward system with the hippocampus

In rodents, both NAcc activation and VTA activation have demonstrated to be dependent on HPC activation. While the NAcc receives direct hippocampal input, VTA activation is indirectly HPC-dependent via a pathway involving the NAcc and ventral pallidum (VP) (Grace, 2012).

The phasic response of VTA DA neurons to salient events (such as rewards) is dependent on the baseline state of DA neuron activity: DA neurons can either be non-firing or show a spontaneous firing in a slow and irregular pattern. As only spontaneously firing DA neurons can respond with burst-firing in response to salient stimuli, the recorded amplitude of a phasic response depends on the number of spontaneously firing neurons (Floresco et al., 2003; Lodge & Grace, 2006). While phasic burst-firing of DA neurons is driven by the peduculopontine tegmentum (PPTg), tonic baseline activity of VTA DA neurons is directly controlled via inhibitory input from the VP (Grace & Bunney, 1985). The VP in turn receives inhibitory input mainly from the NAcc, which receives glutamatergic (excitatory) input from the HPC, particularly from the ventral (in humans anterior) part of the subiculum. Thus, hippocampal activation leads to NAcc activation and NAcc activation leads to VP deactivation. Due to a reduced inhibition from VP more DA neurons are firing spontaneously and can respond with phasic burst-firing in response to salient events. Hence, HPC activity is controlling the amplitude of the phasic DA response via an increase of baseline DA activity (see figure 1; Floresco et al., 2001; Floresco et al., 2003; Lodge and Grace, 2006).

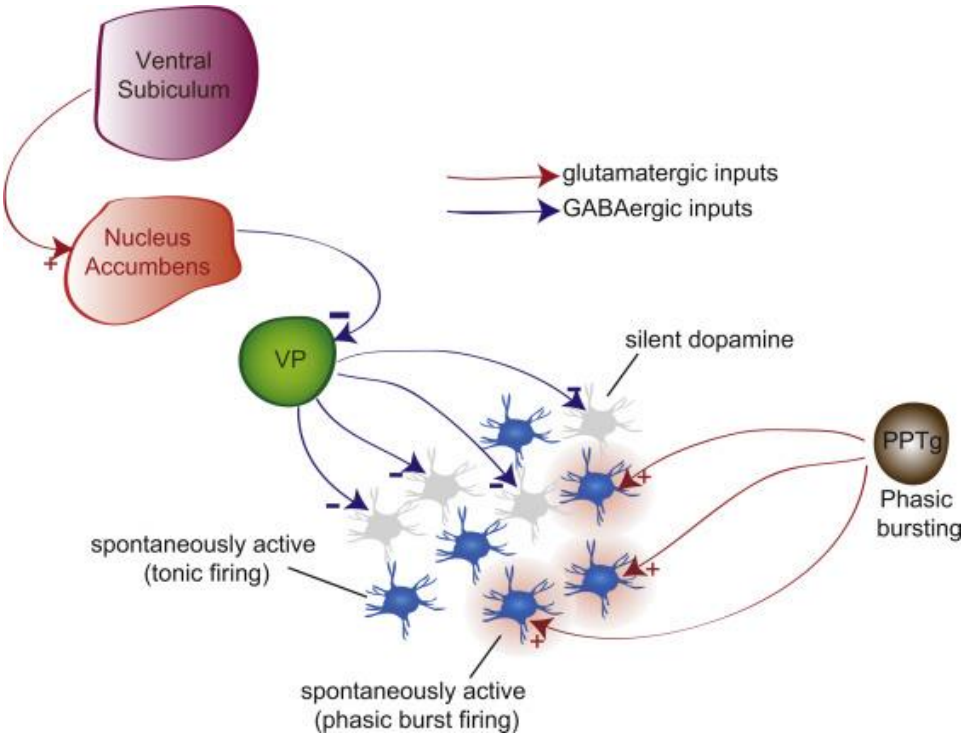


**Figure 1. VTA dopamine (DA) neuron regulation by the ventral subiculum.** DA neurons can either be silent or be spontaneously active (tonic firing). Only spontaneously firing DA neurons can respond with phasic burst-firing driven by the pedunculopontine tegmentum (PPTg). The baseline activity of VTA DA neurons is directly controlled via inhibitory input from the ventral pallidum (VP). The VP in turn receives inhibitory input from the Nucleus Accumbens, which receives glutamatergic (excitatory) input from the hippocampus, particularly from the ventral (in humans anterior) part of the subiculum. *Reprinted from Biological Psychiatry, 81(1), Anthony A. Grace, Dopamine System Dysregulation and the Pathophysiology of Schizophrenia: Insights From the Methylazoxymethanol Acetate Model, pp. 5-8., Copyright (2017), with permission from Elsevier.*

The NAcc receives regulatory input from different limbic (e. g. HPC) and cortical (e.g. PFC) brain regions (Haber & Knutson, 2010), providing the NAcc with contextual information (Jarrard, 1995) and cognitive control to allow goal-directed behavior (Koechlin et al., 2003; Miller, 2000), respectively. It has been argued that both types of input are dependent on selective activation of DA receptors. D1 agonists facilitate HPC drive to the NAcc and do not affect PFC drive to the NAcc. In contrast, D2 agonists attenuate PFC drive to the NAcc without affecting the HPC drive to the NAcc. While limbic input via DA D1 receptor activation is selectively facilitated by phasic DA release, cortical input via DA D2 receptor activation is selectively attenuated by tonic DA release (Goto & Grace, 2005, 2008). Phasic DA release has been shown to occur in response to reward stimuli (Schultz, 2002), thereby affecting limbic drive to the NAcc, whereas omissions of expected rewards have been noticed to reduce tonic DA release (Schultz, 2002), thereby affecting prefrontal drive to NAcc. The first mechanism is assumed to enable the organism to achieve response strategies via reinforcement learning, whereas the second mechanism is considered to mediate behavioral flexibility (Goto & Grace, 2008).

These findings regarding functional interaction between the HPC and the dopaminergic reward system arose from neurophysiological studies in rodents by applying *in vivo* electrophysiological recordings, direct manipulation with stimulation electrodes as well as targeted neurotransmitter injection (Goto & Grace, 2008).

In contrast, functional interactions of these regions are not clear in humans yet. Nevertheless, there are fMRI studies showing functional connectivity of these regions during rest (e.g. Kahn & Shohamy, 2013). Moreover, the influence of reward on memory has often been proven. For instance, it has been demonstrated that reward related activation of dopaminergic midbrain regions (Adcock et al., 2006; Wittmann, 2005; Wolosin et al., 2012) and the NAcc (Adcock et al., 2006) enhanced HPC-dependent memory formation and that the magnitude of behavioral reward modulation was associated with an enhanced connectivity between the HPC and dopaminergic midbrain regions (Wolosin et al., 2012). Increased functional interaction of the VTA/SN with the NAcc and the HPC has also been reported for novel compared to familiar reward-predicting stimuli (Krebs et al., 2011). Therefore, Shohamy and Wagner (2008) suggested that HPC-midbrain interactions support the dynamic integration of experiences (Shohamy & Wagner, 2008).

In another line of research, context-dependent reward stimuli have been used to investigate neurofunctional interactions of the HPC and the dopaminergic reward system. Loh et al. (2015) observed a speeding of response in an object categorization task in trials with rewarding contexts, which was correlated with the connectivity between VTA/SN and HPC. Functional interaction between the HPC and the NAcc could be shown in a yet unpublished study of our research group during context-dependent reward processing in a modified version of the desire-reason dilemma (DRD) paradigm. In this paradigm, some stimuli were conditioned as reward before scanning. Critically, the reward of some of these stimuli depended on the situational context (background). During scanning reward stimuli elicited activation in the VTA and vStr. Additionally, during trials with context-dependent reward stimuli the HPC was activated. Furthermore, HPC and vStr have been found to be positively coupled, particularly in situations in which the context-dependent reward stimulus had to be rejected to achieve the superordinate goal of the task (“desire-reason dilemma” situation).

## 1.2 Pathophysiology of schizophrenia

SZ is a severe mental disorder involving disruptions in thoughts, emotions and behavior. Symptoms of SZ patients are usually divided into two groups: positive and negative symptoms. Positive symptoms are thoughts, perceptions and behaviors which are added to normal experience as for instance delusions, conceptual disorganization, hallucinations, excitement, grandiosity, suspiciousness/persecution, and hostility, whereas negative symptoms are deficits in cognition and in normal emotional and social responding, such as blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking (see Barry et al, 2012; Dean, 2012; Gruber et al., 2014; Kay et al., 1987).

Incidence rates per year range between 0.1 and 0.4 per 1,000 population (Jablensky et al., 1992). Point prevalence ranges between 1 and 17 per 1,000, one-year prevalence between 1.0 and 7.5 per 1,000, and lifetime prevalence between 1 and 18 per 1,000 (Warner & de Girolamo, 1995). Epidemiologic data is summarized in a report of the WHO (Barbato, 1998): Age of onsets typically lies in the early twenties in males and in the late twenties and early thirties in females. Course of illness can vary and reaches from recovering after one or more episodes to unremitting symptoms and increasing disability or to mixed patterns with varying degrees of remission and exacerbations of different length. The disorder can have severe consequences, such as: persisting disability; social rejection, discrimination and social isolation; economic and emotional burden on caregivers; and social costs. Furthermore, mortality is at least twice as high as in the general population.

The term “psychosis” is often used in the context of SZ. Although there is no unified definition for it, psychosis summarizes several symptoms, like hallucinations, delusions and thought disorders leading to reality distortion (Gaebel & Zielasek, 2015). It is a mental state, that can be present not only in SZ but also in diverse psychiatric disorders, such as schizoaffective disorder, BD, and major depression (Pini et al., 2001), as well as in neurological disorders such as Alzheimer’s disease and epilepsy (Arciniegas et al., 2001). In addition, psychosis can be induced by substances/medication such as cocaine, amphetamines, hallucinogens and cannabis (Fiorentini et al., 2011) and other medical conditions such as metabolic disorders (Bonnot et al., 2015).

Although the etiology of SZ is not well understood, there is high agreement on the theory that it results from a complex gene x environment interaction (Wahlberg et al., 1997). As shown by

family, twin, and adoption studies, SZ is highly heritable and many candidate genes have been associated with the disorder. Environmental factors include physical (e.g. complications during pregnancy and birth, infection, and autoimmune disease) as well as psychological factors (e.g. stress and drug abuse) (Dean, 2012).

SZ is often considered as a neurodevelopmental disorder due to findings suggesting that abnormalities already develop in utero during late first or early second trimester and that these abnormalities might then activate pathologic neural circuits during adolescence or young adulthood, finally resulting in the emergence of positive and/or negative symptoms (Fatemi & Folsom, 2009).

There are several hypotheses for the pathophysiology of SZ involving different neurotransmitter systems like DA, glutamate, GABA, and acetylcholine (Dean, 2012). One of the most prominent and influencing hypotheses is the dopamine hypothesis, which states an abnormal dopaminergic neurotransmitter system in psychosis (Howes & Kapur, 2009). The following section will describe this hypothesis and its historical changes.

### 1.2.1 Dopamine hypothesis of schizophrenia

In the first version of the "dopamine receptor hypothesis" van Rossum (1966) suggested a hyperdopaminergic state to be responsible for SZ. In a modification of this hypothesis from Davis et al. (1991), a striatal hyperdopaminergia and frontal hypodopaminergia have been distinguished – accounting for different types of SZ symptoms. Recently, a third version of the dopamine hypothesis has been developed by Howes and Kapur (2009). In this version, new evidence from neurochemical imaging studies, genetic studies, studies on environmental risk factors, studies with subjects displaying high risk of psychosis, and from animal studies is synthesized to provide a framework that links environmental and genetic risk factors to an increased presynaptic striatal dopaminergic function leading to aberrant salience and consequently to psychosis. These three versions of the dopamine hypothesis will be introduced in more detail in this section. Finally, an alternative view of the pathophysiology of SZ is described, which assumes that the dopaminergic system is normal in its configuration and only abnormally regulated by other regions (Grace, 2010a,b, 2012, 2016, 2017).

The original dopamine hypothesis assumed an overall excessive transmission at DA receptors as the cause of SZ and has been based on several findings: First, Carlsson and colleagues (1957) could show that reserpine, an effective drug for the treatment of SZ, blocks the reuptake of DA. Second, it could be shown that psychotic symptoms can be both elicited in healthy individuals

and increased in SZ patients by drugs increasing dopaminergic transmission (Lieberman et al., 1987). Later, a direct relationship between clinical effectiveness of antipsychotic drugs and their affinity for DA receptors could be demonstrated (Creese et al., 1976; Seemann & Lee, 1975; Seemann et al., 1976). And still, DA receptor blocking drugs are the major treatment in SZ (Falkai et al., 2009).

The second version of the dopamine hypothesis from Davis et al. (1991) assumed a regionally specific subcortical hyperdopaminergia and a prefrontal hypodopaminergia and was based on the finding that DA metabolites are not universally elevated or are even reduced in some patients. Moreover, different DA receptors show different brain distributions, with predominant cortical D1 receptors and predominant subcortical D2 receptors. The prefrontal hypodopaminergia was shown by PET studies finding a reduced cerebral blood flow in frontal cortex – a state called "hypofrontality". Davis et al. (1991) hypothesized that the frontal hypodopaminergia is related to the negative symptoms and the striatal hyperdopaminergia is related to positive symptoms (Davis et al., 1991). Both metabolic states seem to be linked to each other, as experiments in animal model show that prefrontal lesions lead to increased striatal DA metabolite levels and D2 receptor density (Pycock et al., 1980). Indeed, application of DA agonists in the prefrontal cortex reduces striatal DA metabolite levels (Scatton et al., 1982). Hyperactivation of the vStr, as an indirect marker of a striatal hyperdopaminergic state, was also found in a recent fMRI study from Richter and colleagues (2015). Additionally, the authors provided evidence for a disturbed top-down control of striatal reward signal by prefrontal brain regions.

The third version of the dopamine hypothesis of Howes and Kapur (2009) consists of four components:

First, the authors suggest that multiple factors like a fronto-temporal dysfunction, genes, stress or drugs interact and result in a DA dysregulation. The interactions of some of these factors have already been established in animal studies (Fulford & Marsden, 1998; Howes et al., 2000; Jones, 1992) and in studies with humans (Pruessner et al., 2004). For example, Pruessner and collegues (2004) could demonstrate that striatal DA release in response to stress is increased in people reporting low maternal care during their early childhood. Furthermore, Howes and Kapur (2009) suggest that DA acts not isolated but in interaction with other neurotransmitter systems like glutamate (Kegeles et al., 2002) and GABA (Wassef et al., 2003). Gene x environment interactions have also been identified as possible causes of DA dysregulation. For example, an increased risk of psychosis is associated with variants of the catechol-O-

methyltransferase gene, which is involved in DA catabolism, interacting with early cannabis exposure (Caspi et al., 2005).

Second, due to advances in neurochemical imaging techniques, it was possible to measure presynaptic DA function. With these techniques, an elevated DA synthesis capacity could be shown in SZ (Hietala et al., 1995, 1999; Howes et al., 2009; Lindström et al., 1999; McGowan et al., 2004; Meyer-Lindenberg et al., 2002; Reith et al., 1994) – moving the focus of the new version of the dopamine hypothesis from DA receptor alterations to a dysregulation at the presynaptic dopaminergic control level.

Third, Howes and Kapur (2009) link the dopaminergic dysregulation to psychosis or "psychosis proneness" rather than SZ. In line with this, an elevated presynaptic striatal DA function is not only seen in patients with SZ, but also in individuals with a high risk of psychosis, such as individuals with schizotypal personality (Abi-Dargham et al., 2004; Soliman et al., 2008) and relatives of SZ patients (Huttunen et al., 2007). Moreover, these individuals show increased psychotic symptoms and DA indices in response to stress (van Winkel et al., 2008).

Fourth and final, Howes and Kapur (2009) assume dopaminergic dysregulation to alter the appraisal of stimuli. In an attempt to explain how clinical expression of the psychiatric illness can arise from dopaminergic abnormalities, the authors refer to findings linking subcortical DA systems to incentive or motivational salience (Berridge & Robinson, 1998; Robbins & Everitt, 1982, 1996). In 2003, Kapur published his view of psychosis as a state of aberrant salience. He suggested that an abnormal DA release and firing of DA neurons lead to an aberrant assignment of salience to innocuous stimuli. According to Kapur (2003), hallucinations and delusions can be considered to emerge over time as the individual`s own explanation of the experience of aberrant salience.

Grace (2010a, b, 2012, 2016, 2017) suggests an alternative view of SZ psychopathology assuming that the dopaminergic system is normal in its configuration and only abnormally regulated by other regions. He states, that despite the long history of antidopaminergic treatment in SZ, clear evidence of a dysfunctional dopaminergic system has not been found and that DA levels have not been consistently shown to be elevated.

The dopaminergic system is not acting isolated. Instead, it is interacting with other neurotransmitter systems like glutamate (Kegeles et al., 2002) and GABA (Wassef et al., 2003). During the last decade, more and more attention has been directed to the role of the glutamatergic system in SZ. In contrast to dopaminergic drugs, glutamatergic drugs have been

demonstrated to evoke a more complex pattern of symptoms, involving also negative symptoms of SZ (Javitt & Zukin, 1991). The pathophysiological role of two regions of the glutamate system has been particularly investigated: the prefrontal cortex and the HPC (Christie et al., 1985; Grace, 1991, 2012; Sesack & Pickel, 1992).

Due to its role in executive functions (Goldman-Rakic,1996), a cognitive domain in which SZ patients show major deficits (Donohoe & Robertson, 2003; Eisenberg & Berman, 2010; Freedman & Brown, 2011; Kerns et al., 2008; Melcher et al., 2014; Reuter & Kathmann, 2004; Velligan & Bow-Thomas, 1999), and its functional connectivity to the dopaminergic system (Haber & Knutson, 2010), the prefrontal cortex is a plausible key region for SZ (Goto & Grace, 2005, 2008). Consistent with this view, functional abnormalities (Fusar-Poli et al., 2007) have been shown for the prefrontal cortex and it`s connectivity (Minzenberg et al., 2009; Richter et al., 2015; Yoon et al., 2013).

The HPC is another glutamatergic key region, which has been investigated extensively and has been shown to play a central role in psychosis. In the following section its role for the pathophysiology of SZ is described in more detail.

### 1.2.2 The role of the hippocampus in the pathophysiology of schizophrenia

Initially, the postmortem finding of a decreased HPC volume in SZ patients (Brown et al., 1986; Falkai et al., 1988; Jakob & Beckmann, 1986) led to the assumption that HPC atrophy plays an important role in the etiology of SZ. In line with that, SZ patients show a deficit in cognitive functions (e.g. semantic memory), which are dependent on the HPC (Kuperberg & Heckers, 2000). However, metabolic imaging studies revealed a hyperactivation of the anterior HPC (Malaspina et al., 1999). Although there seems to be no direct hippocampal input to the dopaminergic neurons in the VTA, neurophysiological studies in rodents revealed an indirect functional connectivity between the HPC and the VTA via the NAcc and the VP (Grace, 2010a, b, 2012, 2016, 2017).

The role of the HPC in the pathophysiology of SZ has already been extensively studied in animal models of SZ. Validity criteria for animal models of SZ are summarized in Jones et al. (2011): For an animal model of SZ, it is important to mimic both behavioral and biological abnormalities usually found in patients. One major problem is that core symptoms of SZ, such as hallucinations and delusions, cannot be assessed in animals (mainly because they are assumed to be unique to humans). Therefore, specific tests have been developed that assess brain functions with translational relevance for the symptoms.

Nearly all the animal models are able to replicate aspects of positive symptoms of SZ. But only a few of them can mimic HPC abnormalities that have been typically found in SZ patients (Jones et al., 2011). Animal models of SZ can be divided into four categories:

1. Lesion-induced animal models: One way to mimic SZ abnormalities in animals is to directly lesion the ventral HPC during neonatal stage (Goto & O'Donnell, 2002; Jones et al., 2011; Lipska, 2004; Lipska & Weinberger, 2000; Tseng et al., 2007, 2009). The neonatal HPC lesioning is meant to disrupt the development of the widespread cortical and subcortical circuitry of the HPC (Lipska & Weinberger, 2000). As adults, those animals show typical behavioral disruptions of animal models of SZ. These abnormalities are (1) hyperresponsivity to stress, DA agonists, and NMDA antagonists (Lipska et al., 1993; Al-Amin et al., 2000); (2) reduced social interactions (Sams-Dodd et al., 1997; Bachevalier et al., 1999a); (3) cognitive deficits, including altered sensorimotor gating (Lipska et al., 1995) and working memory (WM) (Chambers et al., 1996; Bachevalier et al., 1999b). Besides, those animal models revealed a (4) delayed DA system alteration, in terms of abnormal responses in NAcc neurons to activation of their DA afferents, which was absent after treatment with antipsychotic medication (Goto & O'Donnell, 2002).

2. Genetic manipulations: HPC abnormalities have also been observed in genetic models of SZ as in DISC-1 (Jaaro-Peled, 2009), Neuregulin1 (Harrison & Law, 2006; Mei & Xiong, 2008), and Reelin (Krueger et al., 2006; Tueting et al., 2006) knock-out mice.

3. Drug-induced manipulations: HPC abnormalities are also present in pharmacological animal models of SZ using uncompetitive NMDA antagonists like phencyclidine (PCP) (Jentsch & Roth, 1999; Mouri et al., 2007; Neill et al., 2010; Phillips et al., 2001) or dizocilpine (also called MK-801) (Sun et al., 2013; Wiescholleck & Manahan-Vaughan, 2013). PCP is known to induce psychotic episodes in healthy subjects and to exacerbate psychosis in SZ patients (Javitt & Zukin, 1991). As in the previous described animal model, PCP administered rodents show a hyperresponsivity to DA agonists and stress, reduced social interactions (Sams-Dodd, 1996), and deficits in sensorimotor gating and in WM (Grayson et al., 2016). Furthermore, PCP has been noted to interfere with HPC gating of NAcc neuronal activity (O'Donnell & Grace, 1998) and to decrease synaptic spines on cortical and HPC parvalbumin-positive neurons (Jones et al., 2011). In humans, PCP abuse has been reported to be associated with deficits in temporal and frontal regions of the brain (Hertzmann et al., 1990).

4. Developmental animal models: Developmental animal models of SZ are based on the finding that exposure to adverse environmental insults, either during gestation or during the perinatal

period, increases the risk of developing SZ (Jones et al., 2011). One promising developmental animal model which has been used to study SZ is the MAM model (see Grace, 2010a, b, 2012, 2015, 2016, 2017 for a review): In this model lesioning of the HPC is evolved in the adult offspring of rats with an injection of the DNA methylating agent methyl-azoxymethanol acetate (MAM) during pregnancy. The injection is given at a critical developmental time point – at gestational day 17 – which approximates the second trimester of humans. The adult offspring of those MAM injected rats show typical disruptions, such as thinning of limbic cortices with an increased cell packing density, hyper-responsivity to both phencyclidine and to amphetamine as well as disruptions of prepulse inhibition of startle reflex, latent inhibition and deficits in executive function. All in all, this characterizes the MAM model as an effective animal model to study neuronal abnormalities of SZ.

Recordings from the ventral subiculum of the HPC reveal that MAM-treated rats display hyperactivation compared to control rats (Lodge & Grace, 2007). This is in line with the observation of a hyperactivated ventral HPC in patients with SZ (Heckers, 2001; Kegeles et al., 2000; Malaspina et al., 1999; Medoff et al., 2001). Hippocampal activity was previously shown to set DA neurons into a spontaneously firing state. As only spontaneously firing neurons can respond with burst firing when a salient stimulus is present (Floresco et al., 2003; Lodge & Grace, 2006), the HPC is also providing a modulatory "gain" for the burst firing of dopaminergic neurons (Grace, 2012).

The hyperactive state of the HPC seems to arise from a loss of GABAergic interneurons in the ventral subiculum (Lodge et al., 2009). In accordance with this, structural abnormalities of subicular dendrites have been found in subjects with SZ and mood disorders (Rosoklija et al., 2000), as well as a smaller neuron size in hippocampal subfields including the subiculum (Arnold et al., 1995).

## 1.3 Pathophysiology of bipolar disorder

BD is an affective disorder comprising both episodes of depression and episodes of mania. Depressive episodes are characterized by symptoms like depressive mood, sadness or inability to feel emotions; loss of interest; loss of libido; fatigue and reduced energy; sleep disturbances or excessive sleeping; reduced appetize or overeating; difficulties in concentration, memory and/or decision making; feelings of guilt, worthlessness, and/or helplessness; hopelessness and pessimism; restlessness and inner tension; and suicidal thoughts (APA, 2000, 2013). In contrast,

manic episodes are characterized by an inappropriately elevated mood and euphoria or inappropriately elevated irritability and anger; excessive energy and hyperactivity; increased sexual desire; decreased need for sleep; increased talking speed or volume; disconnected and very fast racing thoughts; beliefs of grandiosity and questionable plans and projects; and inappropriate social behavior (APA, 2000, 2013; Barnett & Smoller, 2009).

Episodes of mood symptoms are typically recurrent (Zis & Goodwin, 1979) with even more than 10 episodes in 10-15 % of cases (APA, 1994; Goodwin & Jamison, 1990) and can be either depressive, manic, hypomanic or mixed (Pfennig et al., 2003). According to the ICD-10 classification system (WHO, 1992), all kinds of episodes can occur with or without the presence of psychotic symptoms. Diagnosis of bipolar I disorder requires at least one manic episode in the course of illness. The presence of a depressive episode is not necessary for the diagnosis, although depressive episodes occur in most cases of BD. In contrast, in bipolar II disorder, manic symptoms occur only in a mild form and usually do not cause severe social or occupational impairment – so that diagnostic criteria of a full-blown manic episode are not fulfilled (APA, 2010, 2013).

The epidemiology of BD was summarized by Bauer and Pfennig (2005): Life-time prevalence rates of BD range between 1 and 5%. The disorder can have severe consequences such as increased mortality, with up to 20% of patients dying of suicide. Furthermore, the disorder can have a significant impact on life quality of patients and their families and is often accompanied by work impairment and high costs for the society. The World Health Organisation (WHO) ranked BD as the sixth leading cause of disability worldwide (Lopez & Murray, 1998).

Multiple factors have been proposed to interact to cause BD. Among these are genetic factors. Familial and identical twin studies suggested a strong genetic basis for BD with concordance rates ranging from 40 to 70% and with an estimated heritability of about 90% (Craddock & Sklar, 2013). Results from the genome-wide association study (GWAS) suggest a genetic overlap of BD with SZ (Cross-Disorder Group, 2013), both characterized by polygenic inheritance (International Schizophrenia Consortium, 2009). Variations on the candidate genes catechol-O-methyltransferase (COMT), brain-derived neurotrophic factor (BDNF), neuregulin-1 (NRG-1), and disrupted-in-schizophrenia-1 (DISC-1) associated with risk of psychosis seem to be shared by both disorders (Tiwary, 2012).

Mainly two interrelated prefrontal–limbic functional brain networks have been implicated in the pathophysiology of BD (for review see Maletic & Raison, 2014; Strakowski et al., 2012): Although both networks are related to emotion regulation, the first network is referred to as the

automatic/internal emotional regulatory and the second network is the so-called volitional/external regulatory network. The first network includes the ventromedial PFC, subgenual anterior cingulate cortex (ACC), NAcc, globus pallidus, and thalamus, whereas the second network comprises the ventrolateral PFC, mid- and dorsal-cingulate cortex, ventromedial striatum, globus pallidus, and thalamus. While the first network is assumed to regulate activity in the amygdala in response to endogenously (by memory) generated emotional states, the second network is considered responsible for the regulation of externally induced emotional states.

A disruption of several neurotransmitter systems has been suggested including GABA, glutamate, and several monoamines such as noradrenalin, serotonin and DA (Maletic & Raison, 2014). However, both pharmacological and imaging evidence is pointing to a dopamine hypothesis of BD, which will be described in the following section.

### 1.3.1 Dopamine hypothesis of bipolar disorder

The relevance of the dopaminergic system for both depressive and manic episodes is discussed at least since the formation of the dopamine hypothesis in the 1970s (Singh, 1970; Tissot, 1975; Wittenborn, 1974). While manic episodes are thought to result from an increased dopaminergic neurotransmission due to increased striatal D2/3 receptor availability, reduced dopaminergic function due to increased striatal dopamine transporter (DAT) levels is thought to underlie depression. Switching from one period to the other is assumed to be a failure of DA receptor and transporter homoeostasis, whereby each pathophysiological mechanism might represent an overcompensation of the other (Ashok et al., 2017).

Evidence for this hypothesis is still insufficient. There are studies showing that pharmacological stimulation of the DA system can induce manic symptoms in healthy controls (Asghar et al., 2003; Jacobs & Silverstone, 1986; Nurnberger et al., 1982; Silverstone, 1985) and increase the risk of hypomania/mania in BD patients (Wingo & Ghaemi, 2008). However, an elevated density of D2/3 receptors have only been established for psychotic mania (Pearlson et al., 1995; Wong et al., 1997), while there was no significant difference in the striatal D2/3 receptor density in patients with non-psychotic mania compared to healthy controls (Yatham et al., 2002). The findings regarding DAT density in depression are conflicting. Moreover, both DA agonists and antagonists improve bipolar depressive symptoms (Ashok et al., 2017).

Further evidence comes from animal models of mania and depression. There are several animal models of mania targeting the DA system. For initial animal models, amphetamine was used to

induce hyperlocomotion – an effect that could be reversed by lithium (Berggren et al., 1978; Gould et al., 2001). Stimulation of the DA receptor induced manic-like behavior, reversible by valproate and carbamazepine (Shaldubina et al., 2002). In addition, the DAT knockout rodent model (Perry et al., 2009; Young et al., 2010) and mice with a mutation in a circadian clock gene (Sidor et al., 2015) have been used to mimic symptoms of mania. In mice with mutated circadian clock gene hyperlocomotion was related to an elevated daytime spike in VTA dopaminergic activity, increased DA synthesis and tyrosine hydroxylase activity. Moreover, hyperlocomotion was induced via sustained optogenetic stimulation of the VTA (Sidor et al., 2015). In contrast, Winter et al. (2007) induced depressive behavior in animal models via lesions in dopaminergic areas (VTA/SN) (Winter et al., 2007) and reversed it by stimulation of VTA DA neurons (Tye et al., 2013).

Due to DA's role in reward processing, several fMRI studies investigated the dopaminergic system (in terms of vStr activation) during reward processing in BD patients, providing further indirect evidence for the dopamine hypothesis of BD (Ashok et al., 2017). However, there are also studies in which abnormal activation of the vStr was absent (Bermpohl et al., 2010; Chase et al., 2013; Linke et al., 2012; Sattherthwaite et al., 2015; Singh et al., 2013; Yip et al., 2015). Critically, abnormal reward-related activity of the vStr has also been found in the euthymic phase of illness (Caseras et al., 2013; Dutra et al., 2015; Mason et al., 2014; Nusslock et al., 2012; Trost et al., 2014) and was not uniquely related to manic or depressive phases of illness. Furthermore, a reduced activation of the vStr during reward feedback could be shown in manic (Abler et al., 2008), in euthymic (Trost et al., 2014) and in depressed (Redlich et al., 2015) BD patients. Thus, the hypoactivation of the vStr in response to reward feedback may constitute a state-independent neuroimaging marker of BD. Nevertheless, the findings are partly conflicting and require further replication and disentanglement regarding sample characteristics (e.g. bipolar I/II, medication, fMRI task).

### 1.3.2 The role of the hippocampus in the pathophysiology of bipolar disorder

Current animal models of mania and depression do not focus on the HPC, although there are multiple studies reporting BD-related abnormalities of the HPC. Moreover, cognitive deficits present in BD patients involve deficits of the declarative memory (Altshuler et al., 2004; Bearden et al., 2006; Robinson et al., 2006; VanGorp et al., 1999) – a function highly dependent on the HPC (Eichenbaum, 2000). Therefore, in this section, hippocampal findings in BD patients are summarized.

Findings about structural abnormalities of the HPC are inconsistent, with studies showing a reduced HPC volume (Bearden et al., 2008a; Chepenik et al., 2012; Gao et al., 2013; Mathew et al., 2014; Rimol et al., 2010; Wijeratne et al., 2013), studies showing no significant effect (Altshuler et al., 2000; Avery et al., 2013; Bearden et al., 2008b; Brambilla et al., 2003; Brown et al., 2011; Delaloye et al., 2009; Haukvik et al., 2013; McDonald et al., 2006; Strakowski et al., 1999), and one study showing an increased left HPC volume (Javadapour et al., 2010). Interestingly, psychotic and non-psychotic BD patients did not differ significantly in structural changes of the HPC (Haukvik et al., 2014).

The non-significant findings and findings with small effect sizes of total HPC volume could have possibly arisen from localized deficits within the HPC. Accordingly, when hippocampal subfield volumes were examined separately, post-mortem studies showed a reduced interneuron density (Konradi et al., 2011; Wang et al., 2011) and smaller pyramidal neuron cell bodies (Liu et al., 2007) particularly in the CA1 subregion of the HPC. In vivo structural imaging of hippocampal subfield volumes revealed a volume reduction in CA2/3, CA4/DG, subiculum, and right CA1 in BD patients compared to healthy controls (Haukvik et al., 2015; Mathew et al., 2014). Bearden and colleagues (2008a) reported structural deficits to be most pronounced in the subiculum.

Functional abnormalities of the HPC have been found using fMRI during memory tasks. While Glahn and colleagues (2010) found a reduced HPC activation during recognition in a relational memory task, Whalley and colleagues (2009) reported an increased HPC activation during an emotional memory task. In general, HPC activation seems to be abnormally increased in BD patients in the context of affectively loaded tasks (Chen et al., 2011; Lagopoulos & Malhi, 2007; Malhi et al., 2007; Pavuluri et al., 2007).

Beside structural and functional abnormalities, several studies report glutamatergic and GABAergic abnormalities of the HPC, like disturbances in the ionotropic glutamate N-methyl-D-aspartate receptor (NMDAR) expression and activity (Law & Deakin, 2001; Scarr et al., 2003) and alterations of hippocampal ionotropic $GABA_A$ receptor subunits (Dean at al., 2005).

## 1.4 Neuroimaging to investigate the pathophysiology of psychiatric disorders

In general, the use of neuroimaging techniques is to image the structure, function and neurochemistry of the nervous system (e.g. the brain) (Birur et al., 2017). One powerful and often used technique to investigate the function of the human brain is the functional magnetic resonance imaging (fMRI). As described by Buxton (2009), Huettel and colleagues (2009), as well as Poldrack and colleagues (2011), the MR tomograph uses a strong magnetic field and radio waves to create a 3D image of the brain. The signal intensity within the different parts (voxels) of the created image is dependent on the hydrogen content of the included tissue. The different tissue types of the brain (e.g. gray matter, white matter and cerebrospinal fluid) differ regarding their hydrogen content. Therefore, it is possible to distinguish and visualize the different compartments of the brain. The signal measured in fMRI is the so-called blood oxygenation level dependent (BOLD) signal. When a brain region is active/showing neuronal activity, the amount of oxygenated blood in this region is increased. Not all the blood is needed to supply the cells with oxygen and the relative surplus in local blood oxygenation can be measured using fMRI. Thereby, the magnetic properties of deoxygenated blood are used. Deoxygenated blood is disturbing the magnetic field in that region and the signal is decreasing. In contrast, oxygenated blood is not magnetic and therefore not disturbing the MR signal. In activated regions, the proportion of oxygenated blood relative to deoxygenated blood is increased, with a peak approximately six seconds after the onset of neuronal activity. Therefore, the signal in these regions is increased.

The major advantage of fMRI is its non-invasiveness and that is not dependent on the use of radioactive tracers. Therefore, it can be used multiple times in the same (healthy) living subject without any known long-term side effects (Franko et al., 2008; WHO, 2006). Furthermore, the spatial resolution is relatively high (compared to PET, Near Infrared Spectroscopy (NIRS), ElectroEncephalography (EEG) and MagnetoEncephalography (MEG)), with the pitfall of a relatively low temporal resolution (compared to EEG and MEG). Typical 3-Tesla (T) fMRI scans have voxel size of 3-4 mm (Glover, 2011). However, with now for research available 7-T MR scanners, voxel sizes can be in a resolution of 500 microns or less (Shmuel et al., 2007). The temporal resolution of fMRI scans is limited by the time scale of the hemodynamic response, which has its peak ~5-6 s after stimulus onset. However, inferences about temporal resolution can be made in the 100 ms range, provided that an optimal fMRI task design (including jittering or oversampling of event-related stimuli) and appropriate analysis methods

are used (Buckner et al., 1996; Glover, 2011; Miezin et al., 2000; Ogawa et al., 2000; Sommer & Wichert, 2003). All in all, due to these advantages of fMRI, this technique is used and refined since more than 25 years to study the function of the human brain in healthy subjects and diverse patient populations.

The goal of clinical neuroscience is to investigate the underlying pathophysiological mechanisms that underlie diseases and disorders of the brain. Critically, by using neuroimaging techniques it is possible to detect certain pathophysiological changes before behavioral and/or cognitive changes are detectable (Berk et al., 2009; Ewers et al., 2011; Rose & Donohoe, 2013).

Therefore, neuroimaging is useful in many different ways:

First, it can be used to **find markers that allow an early diagnosis, support clinical diagnosis and/or can be used to predict risk of future illness, illness onset and progress, and treatment outcome**.

Second, neuroimaging markers can **bridge the gap between genes and phenotypes**, and therefore constitute so called **endophenotypes**. Due to the complexity of psychiatric illness, search for specific genetic risk factors was not very successful. Therefore, the concept of endophenotypes was introduced (Glahn et al., 2007). Biological endophenotypes are intermediate phenotypes that are less complex than phenotypes and closer to the action of a specific gene, therefore providing greater power to localize and identify disease-related quantitative trait loci (QTLs) (Blangero et al., 2003; Gottesmann & Gould, 2003). They are correlated with disease liability and independent of the clinical state (presence of symptoms) (Glahn et al., 2007).

Third, besides finding these state-independent markers it is also important to understand how symptoms arise in psychiatric diseases. **Therefore, finding neuroimaging markers that are directly linked to the presence and severity of symptoms is another important goal of clinical fMRI studies.**

Functional integrity of the brain is critical for proper information processing, and disruption of this integrity can result in severe mental problems. Therefore, functional neuroimaging can **provide markers that link molecular processes and mental processes**. In a natural environment, organisms are confronted with different perceptual, cognitive, emotional, social and behavioral challenges. Individuals differ in their way, how they encounter these challenges. And in some individuals this way causes severe problems, which are inherent to psychiatric disorders. Therefore, it is important to understand the mechanisms underlying these processing

using task-based fMRI. During task-based fMRI, the brain can be "observed" during diverse mental processes, while comparing brain activation and connectivity in a specific task or in response to specific stimuli with a control condition not involving the process of interest.

## 1.5 Cross-disorder approach

Although in diagnostic classification systems like ICD-10 and DSM-IV/DSM-V they represent different diagnostic entities, major psychiatric disorders such as SZ, BD and (unipolar) major depression show a significant symptom overlap (Bellivier et al., 2013; Cosgrove & Suppes, 2013; d'Albis & Houenou, 2015; Keshavan et al., 2011; Pearlson et al., 2015; Peralta et al., 2013; Russo et al., 2014; Whalley et al., 2012). For instance, psychotic symptoms are central to the diagnosis of SZ, but they can also occur during bipolar disorder (Cosgrove & & Suppes, 2013; Frangou, 2014). According to Rosen et al. (1983), psychotic symptoms are present in about 50% of manic episodes. Vice versa, mood symptoms, which are a hallmark of BD and (unipolar) major depression, are also present in psychotic episodes of schizophrenia (Cosgrove & Suppes, 2013; Frangou, 2014).

According to the results of meta-analyses of genome-wide association studies (GWAS) for psychiatric disorders performed by the Psychiatric Genomics Consortium (PGC), there is also a remarkable genetic overlap of these disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Thus, it can be assumed that the same genetic variant contributes to the risk of multiple diseases, possibly via shared endophenotypes (Pearlson et al., 2015).

Beside the genetical and phenotypical overlap, there are several neuroimaging abnormalities common in different psychiatric disorders. A meta-analysis by De Peri et al. (2012) revealed significant intracranial, whole brain, total grey and white matter volume reductions and an increased lateral ventricle volume in both SZ and BD. Regions of gray matter reductions are partly overlapping, partly distinct. In general, reductions in gray matter volume are less severe in BD patients compared to SZ patients. While a reduced HPC volume is a relatively robust finding in SZ patients, findings about reduced HPC volume are less consistent in BD patients, with only a few studies showing a decreased HPC volume (Ellison-Wright & Bullmore, 2010).

Although the functional abnormalities of the brain have been investigated in both SZ and BD patients, only a few studies directly compared SZ and BD brain activation. Furthermore, studies investigating functional abnormalities in SZ and in BD often used different tasks with a more

cognitive focus for SZ and a rather emotional focus for BD. Therefore, different neural correlates have been identified for both disorders (d'Albis & Houenou, 2015). Nevertheless, there are also studies investigating the same cognitive processes. For example, facial emotion processing tasks have been used in studies for both disorders. A meta-analysis of those studies revealed different functional abnormalities for SZ and BP patients. While SZ patients showed a hypoactivation of the facial affect processing network and a hyperactivation in visual processing regions, patients with BD overactivated the parahippocampus/amygdala and thalamus and showed a reduced engagement within the ventrolateral PFC (Delvecchio et al., 2013). Studies, in which SZ and BD patients were directly compared with each other have been systematically reviewed by Whalley and colleagues (2012). They found a relative over-activation in the medial-temporal lobe of BD patients compared to SZ patients in emotional and memory tasks.

As previously described, abnormalities of the dopaminergic system and of the HPC are found in both SZ and BD patients. In line with this, patients of both disorders show reward processing abnormalities (Whitton et al., 2015) and many cases of SZ and BD respond to the same medication, e.g. to second-generation antipsychotics (Pearlson, 2015). Especially, reductions of psychotic symptoms have been conclusively shown for this kind of medication, irrespective of the diagnosis (Johnstone et al., 1988). Therefore, some authors consider BD with psychotic features as an intermediate subtype between SZ and BD without psychotic features (d'Albis & Houenou, 2015). Similarly, schizoaffective disorder (SAD) is discussed as another intermediate subtype between SZ and BP, characterized by simultaneous and equally prominent affective and psychotic symptoms (WHO, 1993).

But not only the overlapping features of different psychiatric disorders are of interest. Neuroimaging markers which are able to dissect different diagnostic entities are as well of high relevance. At the moment, the diagnosis often changes during the course of illness. For example, BD patients are often misdiagnosed as being unipolar depressive during their first episode. To find neural predictors of the course of illness, is therefore another important future challenge.

For better therapeutic effects and improved evidence-based guidelines, future diagnostic systems should find new diagnostic boundaries, which are at least partly based on genotype and endophenotype information. Optimal diagnostic criteria should be a good predictor of therapy response, so that diagnostic entities are matching groups of patients responding to a similar treatment. The search for those predictors will be one of the major challenges of the next years.

## 1.6 Research questions

To summarize, abnormalities of the dopaminergic reward system and the HPC have been found for both SZ and BD. However, it is still unclear how the HPC abnormalities relate to the abnormalities of the dopaminergic reward system. While research in animal model of SZ shows that a hyperactivated HPC leads to a hyperdopamergic state, which is related to psychosis, no such animal model exists for BD.

To investigate how HPC activity is related to the abnormal activation within the dopaminergic reward system in SZ and BD, we used a modified version of the desire-reason dilemma paradigm with context-dependent reward stimuli.

The goal of the present thesis is to investigate the role of the HPC during context-dependent reward-processing in human subjects, as well as its dysfunction in SZ and BD patients.

Particularly, we wanted to replicate the previous finding of a hyperactive vStr in SZ and the finding of a hypoactive vStr in BD. Additionally, with the *first study*, we wanted to investigate…

(1) whether goal-directed behavior is more disrupted (in terms of a higher error rate and slower reaction in response during selection of target stimuli) by the presence of a conditioned reward stimulus in SZ patients compared to healthy controls;

(2) whether the hyperactivation of the vStr in SZ patients compared to healthy controls is accompanied by a hyperactivation of the HPC during the presentation of context-dependent reward stimuli;

(3) whether and how the hippocampal (as well as VTA and vStr) activation is related to the psychotic symptom severity of the SZ patients;

(4) whether and how the hippocampal (as well as VTA and vStr) activation is related to behavioral disruption of goal directed behavior;

(5) whether the HPC of SZ patients shows an abnormal coupling with the VTA and/or vStr compared to healthy controls;

(6) whether and how the hippocampal coupling with VTA and/or vStr is related to the psychotic symptom severity of the SZ patients;

(7) whether and how the hippocampal coupling with VTA and/or vStr is related to behavioral disruption of goal directed behavior.

The goal of *second study* was to investigate…

(1) whether goal-directed behavior is more disrupted (in terms of a higher error rate and slower reaction in response during selection of target stimuli) by the presence of a conditioned reward stimulus in BD patients compared to healthy controls;

(2) whether the hypoactivation of the vStr in BD patients compared to healthy controls is accompanied by an abnormal activation of the HPC during the presentation of context-dependent reward stimuli;

(3) whether and how the hippocampal (as well as VTA and vStr) activation is related to the depressive symptom severity of the BD patients;

(4) whether the HPC of BD patients shows an abnormal coupling with the VTA and/or vStr compared to healthy controls;

(5) whether and how the hippocampal coupling with VTA and/or vStr is related to the depressive symptom severity of the BD patients;

(6) and whether and how the behavioral alterations and functional abnormalities of HPC activation and coupling overlap and differ between SZ and BD patients.

# 2 Pathophysiological changes of neurofunctional interaction between the dopaminergic reward system and the hippocampus in schizophrenia

## 2.1 Abstract

Supported by investigations on an animal model of SZ, current hypotheses of SZ pathology assume that the dysregulation of the DA system of the brain might be a secondary consequence of pathophysiological changes in the HPC (Grace, 2010a, b, 2011, 2016, 2017). Critically, although human imaging studies have already shown that the HPC is hyperactivated in SZ (Heckers, 2001; Malaspina, 1999; Medoff, Holcomb, Lahti, & Tamminga, 2001), it is still unclear how this relates to the hyperactive dopaminergic reward system of the patients' brains. Here, we used a modified version of the DRD paradigm (Diekhof & Gruber, 2010), in which context-dependent reward stimuli were used to co-activate the HPC and the dopaminergic reward system. Task-related activity of both the HPC and the VTA/SN was positively correlated with the severity of psychotic symptoms. Furthermore, functional connectivity analyses revealed a dysfunctional coupling of the left HPC with the left VTA/SN. This study provides further evidence, that hyperactivation of the HPC during dopaminergic reward processing and a disrupted functional coupling of the HPC and the VTA/SN may be important pathophysiological mechanisms underlying psychotic symptoms in SZ patients.

## 2.2 Introduction

SZ is one of the most complex and severe mental disorders, involving a disruption of numerous cognitive (Bortolato et al., 2015; Melcher et al., 2014) and emotional (Ventura et al., 2013) processes. Functional disruptions are observed in widespread networks of the patients` brains, depending on the specific task used during neuroimaging (Crossley, et al., 2016). Although the main therapeutic approach for SZ is still the application of neuroleptics, which are known to reduce the DA levels of the brain (Howes & Kapur, 2009), the role of the dopaminergic reward system in the pathophysiology of SZ is still under debate and the pathophysiological processes involved seem to be more complex than assumed.

The dopamine hypothesis of SZ pathophysiology states that the dopaminergic reward system, with the NAcc, as the central node, and the VTA, as the major origin of dopaminergic neurons, is hyperactive (Howes & Kapur, 2009). In line with this hypothesis, findings from studies with

animal models of psychosis (Bardgett et al., 1995; Flagstad, et al., 2004; Lodge & Grace, 2007; Ozawa, et al., 2006; Sumiyoshi, et al., 2005), human post-mortem studies (Purves-Tyson et al., 2017) and human positron emission tomography (PET) and single-photon-emission computed tomography (SPECT) studies (Brunelin et al., 2013) have shown overactivation of the dopaminergic system. SZ patients and individuals with a higher risk of psychosis display heightened presynaptic DA levels (Howes & Kapur, 2009) and an increased amphetamine-induced DA release, which is correlated with worsening of the psychotic symptoms (Grace, 2016).

Supported by investigations on an animal model of SZ, current hypotheses of SZ pathology assume that the dysregulation of the DA system of the brain might be a secondary consequence of pathophysiological changes in the HPC (Grace, 2012; Lodge & Grace, 2007). In this animal model mitotoxin methyl azoxymethanol (MAM) acetate is administered to pregnant rats at gestational day 17 resulting in typical SZ features in the offspring of those rats (Lodge, 2013; Lodge & Grace, 2007, 2009). The pathophysiological changes of the HPC seem to arise from a loss of GABAergic interneurons in the ventral subiculum (Lodge et al., 2009) leading to a hyperactive state of the HPC (Grace, 2012, 2017). HPC hyperactivation leads to overdrive of the NAcc, which inhibits the VP (Grace, 2010a, 2010b, 2012, 2016, 2017). As the VP is regulating the number of VTA DA neurons firing and only active neurons respond to salient stimuli, the amplitude of the stimulus-related signal of the VTA neurons increases with HPC activation (Grace, 2010a, 2010b, 2012, 2016, 2017).

One of the most stable findings of structural brain alterations in SZ is a reduced volume of the HPC (van Erp, 2016), which seems to be already present at first episode (Steen et al., 2006) and even in drug-naïve patients (Chen et al., 2014). In contrast, reduced HPC volume is not present in subjects at clinical high-risk for psychosis, suggesting that there is no reduction in HPC volume before transition to psychosis (Walter et al., 2016). Moreover, HPC structural abnormalities seem to be independent of the patients` illness phase (chronic or first episode) (Adriano et al., 2012). In addition, there are studies showing also functional abnormalities of the HPC (e.g. Fusar-Poli et al., 2007; Jardri et al., 2011; Kühn & Gallinat, 2013), as well as structural (e.g. Abdul-Rahman et al., 2011; Fitzsimmons et al., 2009, 2014; Hanlon et al., 2012; Hao et al., 2009; Kalus et al., 2004; Knöchel et al., 2014; Qiu et al., 2010; Reid et al., 2016; Wu et al., 2015a, 2015b; Yasuno et al., 2005; Zhou, et al., 2008) and functional connectivity abnormalities during resting-state (e.g. Collin et al., 2011; Cui et al., 2015; Duan et al., 2015; Fan et al., 2013; Knöchel et al., 2014; Kraguljac et al., 2016; Lefebvre et al., 2016; Salvador et

al., 2010; Samudra et al., 2015; Shinn et al., 2013; Zhou et al., 2008) and task-based (e.g. Bähner & Meyer-Lindenberg, 2017; Bányai et al., 2011; Diaconescu et al., 2011; Genzel et al., 2015; Henseler et al., 2010; Hutcheson et al., 2015; Meyer-Lindenberg et al., 2005; Schott et al., 2015; Wadehra et al., 2013; Wolf, et al., 2009; Woodcock et al., 2016) fMRI. For example, hippocampal-prefrontal functional connectivity alteration during WM processing is discussed by Bähner and Meyer-Lindenberg (2017) as a possible intermediate phenotype for SZ, as it has been observed in patients, healthy relatives and carriers of two different risk polymorphisms identified in genome-wide association studies. Altered HPC-PFC coupling was also reported in rodent studies in genetic, environmental and neurodevelopmental models for SZ, suggesting that it might also be a promising species-conserved mechanism allowing for translational research (Bähner & Meyer-Lindenberg, 2017). Altered connectivity to the HPC was also shown for the vStr by Schott and colleagues (2015) using a novelty processing paradigm.

Critically, although imaging studies have already shown that the anterior HPC – the human equivalent to the ventral HPC in rodents (Grace, 2016; Grace, 2017) – is hyperactivated in SZ (Heckers, 2001; Malaspina, 1999; Medoff et al., 2001) and that this hyperactivation is associated with psychotic symptoms (Jardri et al., 2011; Silbersweig, 1995), which are believed to rely on a DA-dependent process (Belujon & Grace, 2008), it is still unclear how the HPC relates to the hyperactive dopaminergic reward system of the patients' brains.

It has been hypothesized that functional connectivity between the HPC and the dopaminergic reward system may be important for processing of potentially relevant stimuli (e.g. rewards) dependent on a specific behavioral context (Fanselow, 2000; Grace, 2010a, 2010b, 2012; Jarrard, 1995; Maren, 1999; Maren & Holt, 2000). The HPC` role in memory and context processing has often been shown (Holland & Bouton, 1999; Mizumori et al., 1999, 2007; Myers & Gluck, 1994; Rudy, 2009; Rugg et al., 2012; Sharp, 1999; Smith & Bulkin, 2014; Smith & Mizumori, 2006). Besides, research in rodents suggests that, mediated by the HPC, the VTA shows a higher response magnitude for stimuli in a threatening situation compared to a benign situation (Grace, 2010a, 2010b, 2012, 2016).

In human imaging studies, phasic activation of the NAcc/vStr and VTA is typically observed in reward paradigms, like the monetary incentive delay task (MID; Knutson et al., 2001) and the DRD paradigm (Diekhof & Gruber, 2010), in response to and in anticipation of a reward. In a yet unpublished study of our group, additional HPC coactivation could be demonstrated during the presentation of context-dependent conditioned reward stimuli compared to context-independent reward stimuli. In this study a modified version of the DRD paradigm was used,

which was previously applied in fMRI studies with healthy controls (Diekhof & Gruber, 2010; Diekhof et al., 2012a, 2012b; Krämer & Gruber, 2015; Trost et al., 2016; Wolf et al., 2016) and psychiatric patient populations (Goya-Maldonado et al., 2015; Richter et al., 2015; Trost et al., 2014) to investigate both the bottom-up dopaminergic reward signal and the top-down regulation by the PFC. According to the results of these studies, bottom-up activation of the reward system is present, if a previously conditioned reward stimulus occurs. Compared to situations in which the reward stimulus can be freely chosen ("desire situation"), there is a significantly reduced activation of the vStr and an increased negative coupling of the vStr with the anteroventral prefrontal cortex (avPFC) in situations in which the reward stimulus has to be rejected to achieve a superordinate goal ("desire-reason dilemma"), suggesting a downregulation of the dopaminergic reward system by the PFC.

To investigate the HPC' activation and connectivity with the dopaminergic reward system in patients with SZ, we used the previously described modified version of the classical DRD-paradigm with context-dependent reward stimuli, that was established in a yet unpublished study with healthy controls. To use this paradigm in a patient population, we reduced the complexity and the WM load of the task. We hypothesized that the vStr would be hyperactivated during the presentation of context-dependent reward stimuli, replicating previous results (Richter et al., 2015), and that additionally the HPC would be hyperactivated.

## 2.3 Methods

### 2.3.1 Subjects

20 patients with SZ or schizoaffective disorder and 20 healthy controls were included in this study. The two groups were matched for sex and age. As the groups were not successfully matched for educational level, years of education were introduced as a covariate in all analyses.

Patients were recruited from inpatient and outpatient settings of the Department of Psychiatry and Psychotherapy, University Medical Center Göttingen. Their diagnoses were consented with the treating psychiatrists.

**Table 1.** Demographical and clinical characteristics of the subjects.

| | | | Schizophrenia patients | Healthy controls | *p* value |
|---|---|---|---|---|---|
| Sample size | | | 20 | 20 | |
| Gender (% female) | | | 35.0 | 55.0 | .21[b] |
| Age at time of testing (years) | | | 35.5 ± 10.5 | 31.3 ± 12.00 | .24 |
| Handedness (% left handed) | | | 15.0 | 0.0 | .30[b] |
| Education (years) | | | 13.0 ± 2.7 | 15.2 ± 2.8 | .01* |
| MWT-A | | | 30.4 ± 3.1 | 31.3 ± 1.7 | .29 |
| BDI II | | | 15.5 ± 10.5 | 3.3 ± 5.6 | .00* |
| CGI | | | 4.1 ± 1.0 | | |
| PANSS total | | | 59.1 ± 18.6 | | |
| PANSS positive | | | 12.3 ± 5.5 | | |
| PANSS negative | | | 15.6 ± 6.2 | | |
| PANSS general | | | 31.2 ± 10.6 | | |
| PANSS psychotic[a] | | | 4.8 ± 3.0 | | |
| Age of onset (years) | | | 23.7 ± 8.7 | | |
| Duration of illness (years) | | | 10.8 ± 8.1 | | |
| Medication (absolute frequency) | Neuroleptics | Atypical neuroleptics | 18 | | |
| | | Atypical and typical neuroleptics | 2 | | |
| | Anti-depressants | SSRI | 6 | | |
| | | SSNRI | 4 | | |
| | | Tricyclics | 1 | | |
| | | Tetracyclics | 1 | | |
| | Mood stabilizer (Lithium) | | 3 | | |
| | Benzodiazepine | | 3 | | |
| | Anticholinergics | | 2 | | |
| | β-blockers | | 1 | | |
| | Anticonvulsives | | 1 | | |

*Abbreviations:* BDI, Beck Depression Inventar; CGI, Clinical Global Impression Scale; PANSS, Positive and Negative Syndrome Scale; MWT-A, Mehrfachwahl-Wortschatz Intelligenztest (multiple-choice vocabulary intelligence test); SSNRI, Selective Serotonin-Norepinephrine Reuptake Inhibitors; SSRI, Selective Serotonin Reuptake Inhibitor. * significant group difference ($p < .05$) [a] PANSS subscale summing hallucination and delusion scores [b] *P* values for group differences determined by the non-parametrical Mann-Whitney test.
Unless otherwise indicated: Data are presented as mean ± standard deviation. *P* values for group differences were determined by an independent samples t-test (two-sided).

Patients and healthy subjects were excluded from participation in cases of current drug abuse, current or anamnestic substance-related addiction and neurological disease. Symptom severity was assessed the day before scanning with the PANSS (Kay et al., 1987), Beck Depression Inventar (BDI II; Beck et al., 1996) and Clinical Global Impression Scale (CGI; Guy, 1976).

Using the PANSS, current severeness of positive and negative symptoms as well as of general psychopathology is rated based on a semi-structured clinical interview. Dependent on the total PANSS score, criteria for mild severeness/remission (≤ 60), moderate (≤ 75) and severe illness (> 75) have been defined by Leucht and colleagues (2005) as well as Opler et al. (2007). According to this definition, 13 SZ patients fulfilled the criteria for mild severeness/remission, whereas the illness in the remainder could be categorized as being moderate (n = 1) to severe (n = 6). Based on the CGI severeness scale, seven SZ patients have been rated as mildly ill, six patients as moderately ill, five patients as markedly ill, and two as severely ill. Regarding depressiveness, five patients fulfilled criteria for minimal depression (score 0-13), ten patients fulfilled criteria for mild depression (score 14-19), three fulfilled criteria for moderate depression (score 20-28) and two fulfilled criteria for severe depression (score 29-63). Detailed sample characteristics can be seen in table 1.

### 2.3.2 Experimental protocol

The task performed during scanning was a modified version of the DRD paradigm, which was previously used to investigate bottom-up activation and downregulation of the reward system (Diekhof & Gruber, 2010; Diekhof et al., 2012a; Diekhof et al., 2012b; Goya-Maldonado et al., 2015; Richter et al., 2015; Trost et al., 2014; Trost et al., 2016; Wolf et al., 2016). In this task, depending on the situation, conditioned reward stimuli must be accepted or rejected.

In the conditioning phase, one day before scanning, the subjects had to select one out of two simultaneously presented colored ellipses, by pressing the left or the right button (with right index or middle finger) for choosing either the left or the right stimulus, respectively. They learned that the selection of stimuli with specific colors (red and yellow) is associated with winning ten points. Critically, the outcome of selecting these stimuli depended on the context, in which they were presented. Subjects were instructed that the selection of some stimuli is rewarded, when the stimuli are presented on an “Arctic” background photograph and the selection of other stimuli is rewarded, when those appear on a “Mountain” photograph.

During the first conditioning session, 80 stimulus pairs were presented in front of the “Arctic” background. The reward stimulus for that context was presented in 20 of these stimulus pairs

(10 times on the left side, 10 times on the right side). The subjects had to correctly accept the reward stimulus in at least 75 % of the trials. Otherwise, another block of 4 trials (incl. one reward trial) was added, until the 75 % criterion was reached. Afterwards, they performed the second conditioning session with the "Mountain" background in the same manner.

Beside the two context-dependent reward colors, four neutral colors were paired with each other or with the reward stimulus. The two context-dependent reward-stimuli were presented during both conditioning sessions. Nevertheless, the reward (10 points) for a specific color was delivered only at one context, whereas the same stimulus was neutral (0 points) in the other context. There was no time limit for the response. Presentation of the stimulus pairs lasted until the subjects responded.

During the fMRI scan subjects performed a task, in which they, similar to the conditioning phase, had to select one out of to simultaneously presented colored stimuli. At the beginning of each block of eight trials a target stimulus (one of the four neutral stimuli of the conditioning phase) was introduced. This stimulus had to be chosen, if present, during the subsequent eight trials. Subjects were informed that they would get 60 points at the end of the block for collecting all the targets present in the respective trials. Missing one of the targets caused a loss of all target points. Additionally, subjects could get ten bonus points for collecting a stimulus, which was rewarded during the previous conditioning phase of the experiment (bonus stimulus). When the bonus stimulus was paired with a target stimulus, they could either decide for an immediate but small reward or pursuit the long-term goal of getting a higher reward. Subjects were informed that the points collected during scanning would be afterwards transferred to money (up to 30€).

Pairings of a bonus stimulus with a neutral stimulus constituted the "desire situation", as the bonus stimulus could be freely chosen. Contrary to this, in the "desire-reason dilemma" the conditioned stimulus was paired with a target stimulus. Selecting the "desired" bonus stimulus was not reasonable in this situation, as the subject would have lost all the target points. While, the desire situation can be used to investigate bottom-up activation of the reward system, the desire-reason dilemma has been shown to be an appropriate condition for the investigation of (top-) down-regulation of the reward system, especially of the vStr, by the avPFC (Diekhof & Gruber, 2010; Diekhof et al., 2012a, 2012b; Goya-Maldonado et al., 2015; Richter et al., 2015; Trost et al., 2014; Trost et al., 2016; Wolf et al., 2016).

The stimuli were presented in front of one of two background photographs (in the following designated as "contexts"), varying between (but not within) the blocks of trials. As previously

learned in the conditioning phase, the rewarding of bonus stimuli depended on the respective context. As a consequence, bonus stimuli could either be presented in front of the correct context, yielding a bonus of 10 points when collected ("desire situation"), or in front of the incorrect context, yielding no additional bonus.

Figure 1 depicts an example of the experimental trial sequence. Each block of trials started with the presentation of the background photograph. After 600 ms the target stimulus for the subsequent trials was presented, disappearing after 1,800 ms. Another 600 ms later the first stimulus pair appeared for 2,500 ms. During this period the subject had to press one of the two buttons for selecting either the left or the right stimulus. The next stimulus pair was presented after a fixed interstimulus interval (ITI) of 600 ms. Stimulus duration and ITI added up to a total trial length of 3,100 ms. The trial duration was optimized to capture the BOLD response, by the creation of varying time lags between trial onset and scan onset (interscan interval of 1,800 ms). After eight trials of different stimulus pairs a feedback was presented for 2,800 ms. The duration of one block was 30.6 s.

The combination of the different stimulus types yielded the following six conditions: non-target paired with non-target (N-N), non-target paired with target (N-T), non-target paired with a bonus stimulus that is reward-associated in the respective context (N-CV10/"desire situation"), non-target paired with a bonus stimulus with reward-association in the other context (N-CV0), as well as target paired with a bonus stimulus that is reward-associated in the respective context (T-CV10/"desire-reason dilemma") and target paired with a bonus stimulus with reward-association in the other context (T-CV0). In total, subjects performed 48 blocks (24 blocks for each context) of eight trials during scanning. Each neutral color served as a target twelve times and each stimulus type was presented equally often at the left and at the right side. Positions within the block and transitions from trial to trial were counterbalanced for each condition.

All subjects practiced the task one day before and immediately before scanning. First, the task was explained during some example trials until the subject fully understood the task. Second, a training session followed with 8 blocks of 8 trials with low speed (target presented for 3 s and stimulus pair presented for 4 s). And third, a training session with 16 blocks of eight trials was conducted with the speed of the scanning sessions (target presented for 1.8 s and stimulus pair presented for 2.5 s). The subjects had to reach several criteria of task performance, otherwise more blocks of trials were added. The last training session was repeated on the next day right before scanning. With this extensive training, we could make sure that all the subjects – even

the patients – reached an appropriate level of correctness during scanning (≥ 18 correct trials per condition). This is of high relevance for a proper analysis of behavioral and fMRI data.

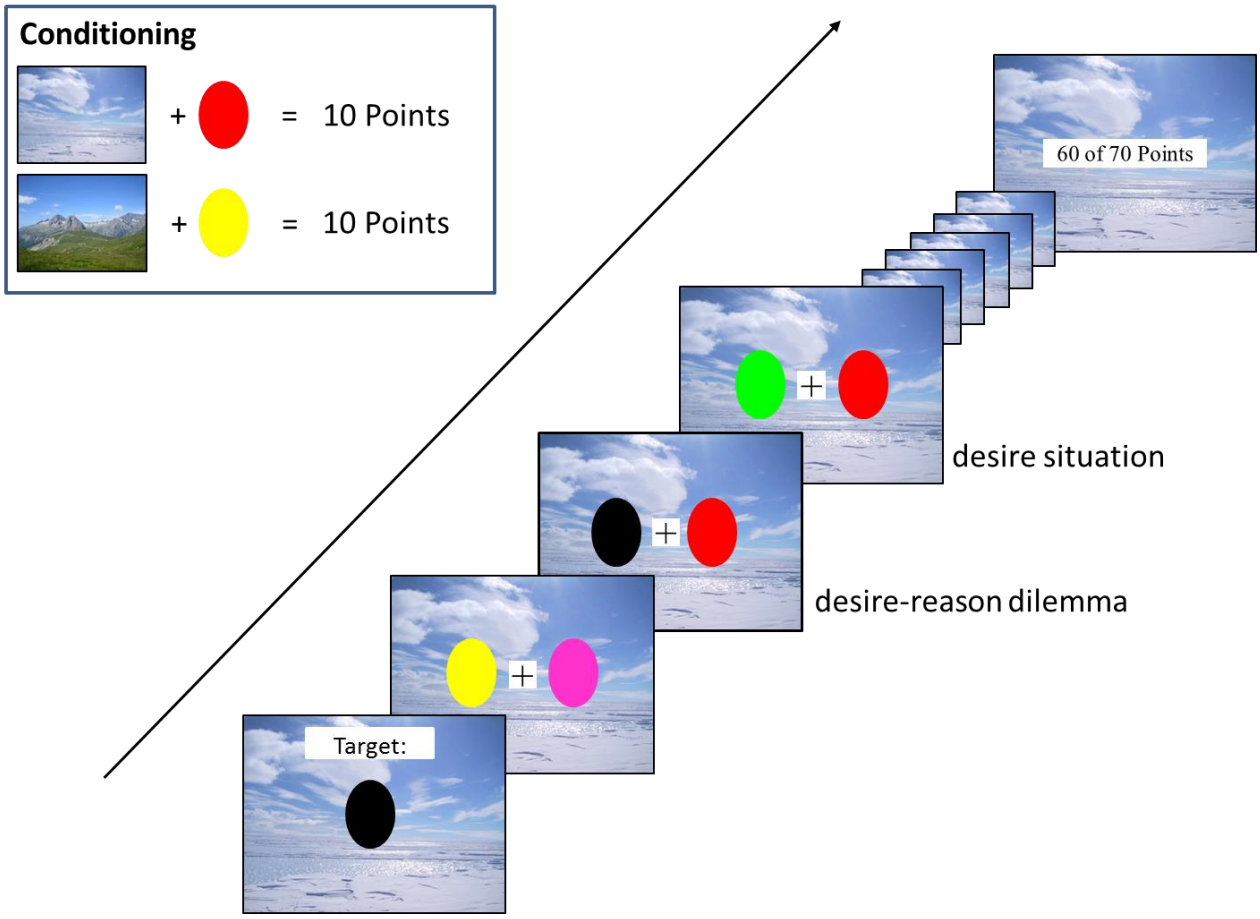


**Figure 2.** Example of the experimental trial sequence: At the beginning of each block of trials a target stimulus was introduced. This stimulus had to be chosen, if present, during the subsequent trials. Subjects were informed that they would get 60 points at the end of the block for collecting all the targets present in the respective trials. Missing one of the targets caused a loss of all target points. Additionally, subjects could get ten bonus points for collecting a stimulus, which was rewarded during the previous conditioning phase of the experiment (see upper left part of the figure). The rewarding of those bonus stimuli depended on the context (background photograph), in which they were presented. Pairings of a bonus stimulus with a non-target constituted the "desire situation", as the bonus stimulus could be freely chosen. Contrary to this, in the "desire-reason dilemma" the conditioned stimulus was paired with a target stimulus and had to be rejected to achieve the superordinate goal of the task.

### 2.3.3 fMRI acquisition

A total of 825 volumes was acquired in three functional runs using an echo planar imaging (EPI) sequence (interscan interval (TR): 1,800 ms; echo time (TE): 30 ms; flip angle: 70°) with an 8-channel head coil in a 3T Siemens TRIO MRI scanner (Siemens Healthcare, Erlangen, Germany). 34 axial slices parallel to the anterior commissure-posterior commissure line were

obtained in ascending acquisition order (voxel size: 3x3x3 $mm^3$, interslice gap: 20 %) using a gradient-echo echo-planar imaging (EPI) sequence (field of view: 192 mm, matrix size: 64x64). Stimuli were presented via goggles and subjects responded via button press on a fiber optic computer response device. Stimulus delivering and synchronization with scanner was conducted through the Presentation® Software (Neurobehavioral Systems, Albany).

### 2.3.4 Behavioral data analysis

The behavioral data were analyzed using IBM SPSS statistics for Windows, version 24 (SPSS Inc., Chicago, IL). Mean RTs and error rates have been defined at single-subject level. To calculate the effect of the presence of a bonus stimulus on goal-directed behavior during target selection, we compared RTs and error rates of "desire-reason dilemma" situations (T-CV10) with RTs and error rates in trials with targets that were paired with non-targets (N-T).
RTs and error rates were analyzed using a mixed 2*2 ANOVA model with task condition (N-T, T-CV10) as a within-subject factor and group (healthy controls, SZ patients) as a between-subject factor. Only RTs of correct trials were included in the analysis, whereby errors were defined as choosing the non-target or bonus-stimulus in presence of a target, or giving no response at all (omissions). All tests were thresholded at $p < .05$, two-sided.

### 2.3.5 fMRI data analysis

Preprocessing and statistical analyses of functional data were performed with SPM8 (Wellcome Department of Imaging Neuroscience, London, UK). Preprocessing comprised realignment and unwarping, correction for slicetime acquisition differences (reference slice: 1) and low frequency fluctuations, normalization into standard stereotactic space (to the Montreal Neurological Institute (MNI) skull-stripped structural template), and spatial smoothing with a Gaussian kernel of 8 mm FWHM.

For the 1st level statistical analysis of the functional images, the onsets of the experimental conditions as well as for the cue and feedback events were modelled by the convolution with a hemodynamic response function accounting for the delay of the BOLD (blood oxygen level-dependent) response. For each subject, statistical images were computed for each condition against an implicit baseline.

For the 2nd level statistical analysis, these first-level images were included in a two-way ANOVA with group (SZ patients, healthy controls) as a between-subject factor and condition as a within-subject factor. Furthermore, the variable "years of education" was included as a "covariate of no interest". Effects of the conditions where then calculated for each group

separately using t-contrasts. For purposes of comprehensibility, we limited our analyses to the contrast of the "desire situation". To separate reward-related brain activity from other activity not related to reward processing but to motor, sensory or decisional processes, we compared the brain activation during the "desire situations" with brain activation during trials with only neutral stimuli (N-N). Group comparisons of the statistical images were calculated using t-contrasts.

To assess the correlation of psychotic symptoms (e.g. summed PANSS items scores for hallucinations and delusions) and activation of the vStr, the VTA/SN, and the subiculum of the HPC, the patients` PANSS psychotic scores were used as covariates of interest in an additional one-sample t-test. For this one-sample t-tests first-level images contrasting N-CV10 trials with N-N trials were included. Again, the variable "years of education" was included as a "covariate of no interest".

Furthermore, we wanted to assess whether higher reward-related activity is related to the degree of distraction by the reward stimulus – operationalized as the difference between RT and error rates during trials with a target paired with a non-target (no distraction) and trials with a target paired with a reward-stimulus (distraction). These RT and error rate differences were used in additional one-sample t-tests as covariates to assess their correlation with activation of the vStr, VTA/SN and HPC. These analyses included first-level images contrasting N-CV10 trials with N-N trials and "years of education".

To assess the reward-related functional coupling, we calculated psycho-physiological interactions (PPIs). Using PPIs, correlations of activation between two brain regions depending on a psychological state (like reward-processing) can be assessed. For PPI analyses, the time course of activation is extracted from a seed region. Afterwards, an "interaction regressor" is calculated as the product of the task time-course and the activation time-course of the seed region.

Due to our *a priori* anatomical hypotheses, we used a p-value of .05, FWE-corrected for small-volume, as a statistical threshold. Regions of interest were defined using boxes (12x12x12 $mm^3$) around left and right vStr and VTA coordinates from Diekhof & Gruber (2010) and using anatomical masks for the left and right subiculum of the HPC created by the SPM Anatomy Toolbox (version 2.0).

## 2.4 Results

### 2.4.1 Behavioral data

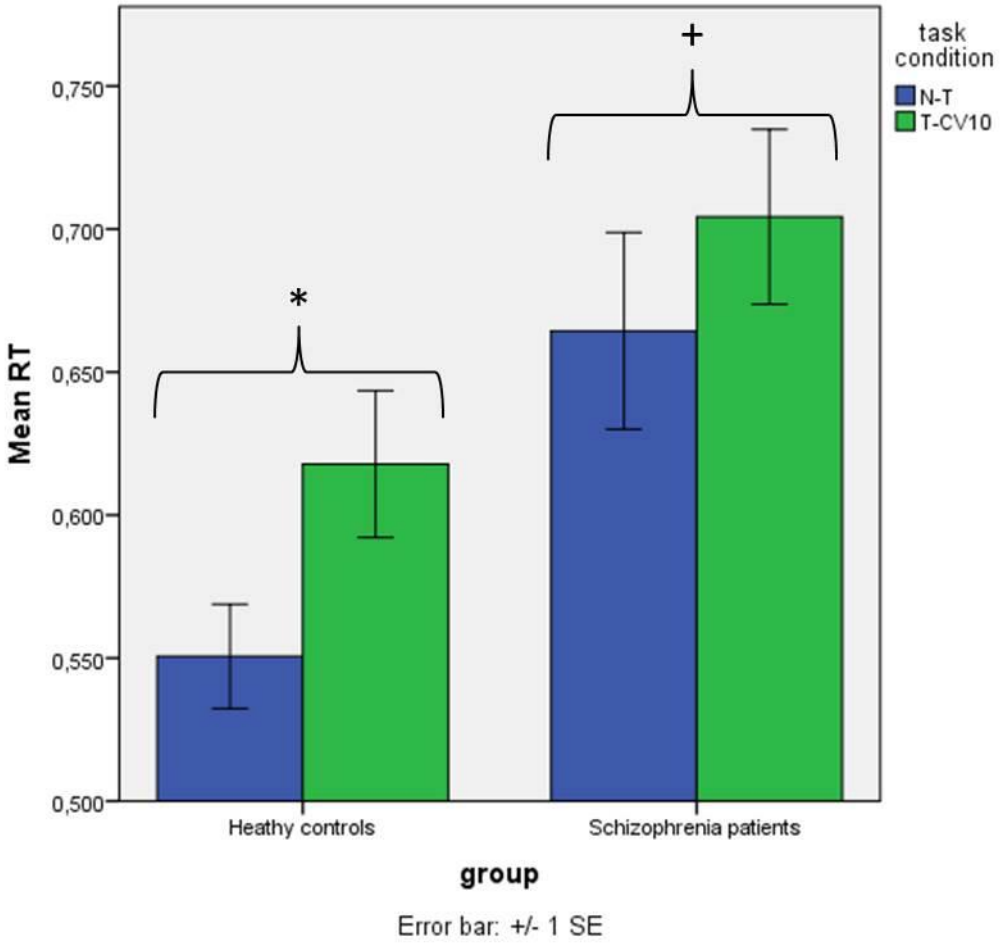


**Figure 3.** Mean reaction time (RT) of healthy controls and schizophrenia patients (± standard error (SE)). The RT in trials with targets paired with a conditioned reward stimulus (T-CV10) was significantly increased compared to trials with targets paired with a non-target (N-T) in healthy controls, whereas there was only a difference at trend level in schizophrenia patients. * $p < .001$; $^{+}$ $p = 0.063$

For RTs, both main effects reached the significance level (task condition $F(1,38) = 20.242$, $p < .001$, $\eta^2 = .348$; group $F(1,38) = 7.101$, $p < .05$, $\eta^2 = .157$). The interaction effect was not significant. The main effect of task condition was driven by a relative RT slowing during target selection when a reward stimulus was present, while the main effect of group was driven by relatively slower RTs in the SZ group compared to healthy controls. Within-group comparisons revealed a significant RT difference between task conditions in healthy controls ($p < .001$), whereas the RTs differed only at trend level in SZ patients ($p = .063$) (see figure 3).

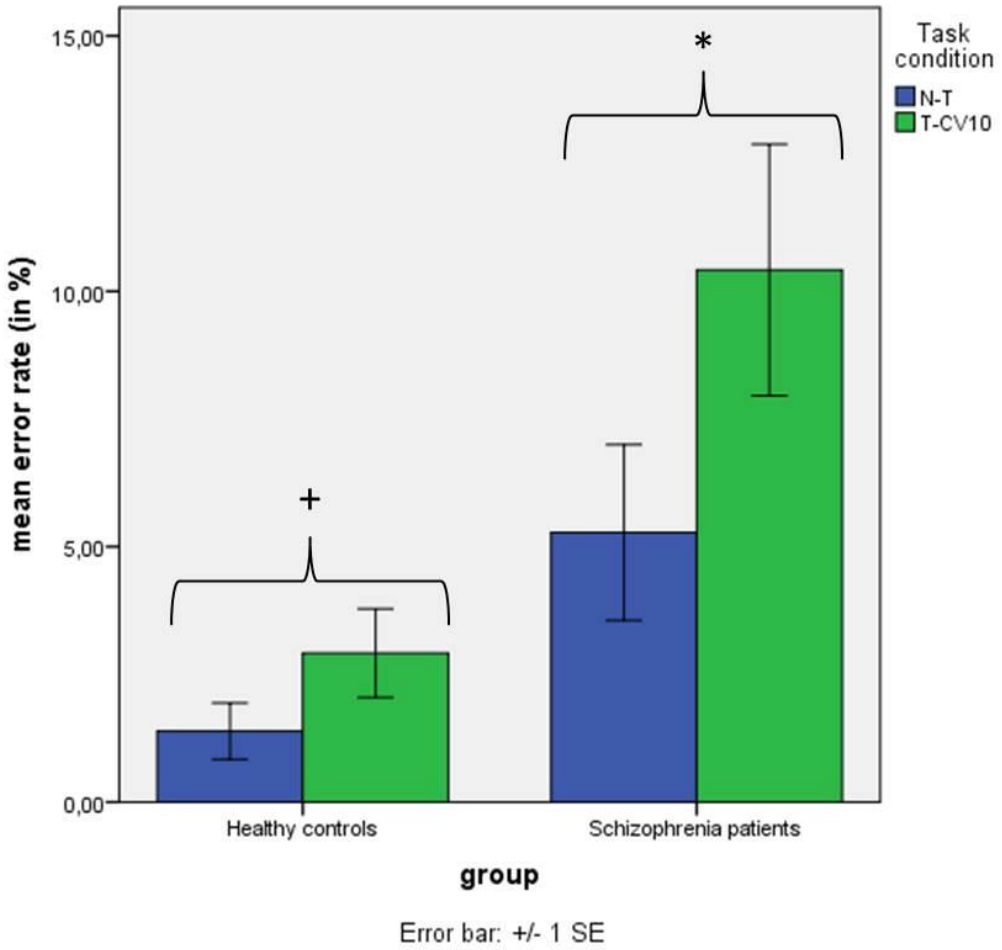


**Figure 4.** Mean error rate of healthy controls and schizophrenia patients (± standard error (SE)). The error rate in trials with targets paired with a conditioned reward stimulus (T-CV10) was significantly increased compared to trials with targets paired with a non-target (N-T) in schizophrenia patients, whereas there was only difference at trend level in healthy controls. * $p < .01$; $^{+}$ $p = 0.069$.

For error rates, again, both main effects reached the significance level (task condition $F(1,38) = 11.799$, $p < .001$, $\eta^2 = .237$; group $F(1,38) = 7.930$, $p < .01$, $\eta^2 = .173$). The interaction effect was not significant, although there was a non-significant trend for an interaction ($F(1,38) = 3.462$, $p = .071$, $\eta^2 = .083$). Post hoc comparisons revealed that the main effect of task condition was driven by a higher error rate during target selection when a reward stimulus was present, while the main effect of group was driven by higher error rate in the SZ group compared to healthy controls. Furthermore, there was a non-significant tendency of a higher increase in error rate in response to target stimuli in the presence of a conditioned reward stimulus in SZ patients compared to healthy controls. Within-group comparisons revealed a significant error rate difference between task conditions in SZ patients ($p < .01$), whereas the error rates differed only at trend level in healthy controls ($p = .069$) (see figure 4).

### 2.4.2 fMRI data

During trials in which context-dependent reward stimuli were paired with neutral stimuli ("desire-situation"), all the regions of interest (ROIs) were significantly activated (see table 2). Both healthy controls and SZ patients showed an activation of the bilateral HPC, the bilateral VTA/SN and the bilateral vStr. Replicating findings of a previous study (Richter et al., 2015), the left vStr was hyperactivated in patients (see table 2, for whole-brain results see Supplement Table S1).

Although there was only a subthreshold hyperactivation of the VTA/SN and the HPC, the severity of psychotic symptoms (PANSS psychotic) was significantly correlated with left HPC activation (Figure 5a), and bilateral VTA/SN activation (Figure 5b). VStr activation was not significantly correlated with the severity of psychotic symptoms.

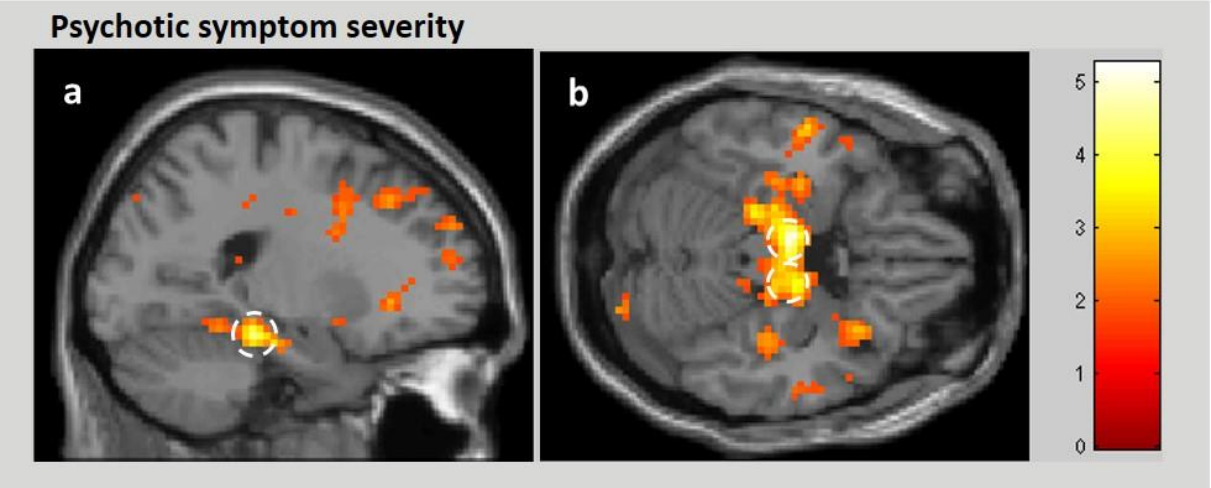


**Figure 5.** Correlation of the severity of psychotic symptoms (PANSS psychotic) with a) left HPC activation (left [-21 -31 -17] t = 4.31) and b) bilateral VTA/SN activation (left [-9 -13 -20] t = 5.25, right [12 -13 -20] t = 3.63) during "desire situations". For illustrational purposes, p level was set at .05, uncorrected.

The previously described RT slowing in response to targets, when a reward stimulus was present, was positively correlated with left VTA/SN activation ([-15 -25 -23] t = 3.16). Moreover, there was a significant negative correlation of RT data with right HPC activation ([30 -22 -23] t = 3.62). The increased error rate in response to targets, when a reward stimulus was present, was positively correlated with right vStr activation ([12 8 1] t = 3.76). Negative correlations were not significant.

To elucidate the functional interaction of the HPC and both the VTA/SN and the vStr, we calculated psycho-physiological interactions (PPIs) using spheres (radius 3 mm) around coordinates of the local maxima of the patients' HPC activation as seed regions:

**Table 2** Reward-related brain activations in the "desire situation" in schizophrenia patients compared to healthy controls

| **Region** | **Schizophrenic patients**<br><br>MNI coordinates (*t*-values) | **Healthy controls**<br><br>MNI coordinates (*t*-values) | **Schizophrenic patients > Healthy controls**<br>MNI coordinates (*t*-values) | **Healthy controls > Schizophrenic patients**<br>MNI coordinates (*t*-values) |
|---|---|---|---|---|
| L vStr | -18 8 -2 (4.78)* | -9 8 -5 (4.50)* | -18 8 -11 (3.00) | n.s. |
| R vStr | 18 11 -5 (4.55)* | 12 8 -2 (4.53)* | [18 14 -5 (1.83)]<br>*[21 14 -5 (1.84)]* | [6 -17 -2 (2.03)] |
| L VTA/SN | -6 -25 -11 (4.16)<br>*-6 -25 -8 (4.32)* | -12 -22 -11 (4.00) | [-6 -25 -11 (1.80)]<br>*[-9 -28 -8 (2.23)]* | n.s. |
| R VTA/SN | 15 -25 -14 (3.86)<br>*21 -31 -17 (5.11)** | 15 -22 -11 (4.01)<br>*18 -19 -11 (4.50)** | [9 -25 -14 (1.83)] | n.s. |
| L HPC | -18 -31 -11 (4.18)<br>-27 -28 -17 (3.10) | -24 -28 -17 (4.16) | [-15 -31 -11 (1.87)] | n.s. |
| R HPC | 21 -28 -17 (4.65)<br>*21 -31 -17 (5.11)** | 21 -31 -8 (4.53)* | [21 -28 -17 (1.98)]<br>*[21 -28 -20 (2.46)]* | n.s. |

*Abbreviations:* HPC, hippocampus; L, left; MNI, Montreal Neurological Institute; n.s., not significant; R, right; SN, substantia nigra; vStr, ventral striatum; VTA, ventral tegmental area.

If not indicated differentially, effects on regional brain activation were significant at a level of $p < .05$, FWE-corrected for the small volume. * Brain activations, which are additionally significant at a level of $p < .05$, FDR-corrected for whole brain. For purposes of completeness and better understanding local maxima outside the defined ROI are reported italicized and we also report subthreshold effects ($p < .05$, uncorrected) using square brackets.

PPI analyses revealed a significant positive **coupling of left HPC** with the left VTA/SN (left [-6 -16 -23] t = 3.43) in healthy controls. This positive coupling was not present in SZ patients. Furthermore, SZ patients showed a negative coupling of the left HPC with the right vStr (right [18 14 -11] t = 3.37), which was not observable in healthy controls. While group comparisons on these findings did not reach significance level, the coupling of the left HPC to the bilateral

VTA/SN showed a significant negative correlation with the severity of psychotic symptoms (left [-9 -13 -17] t = 3.25, right [3 -19 -14] t = 3.95, see figure 6).

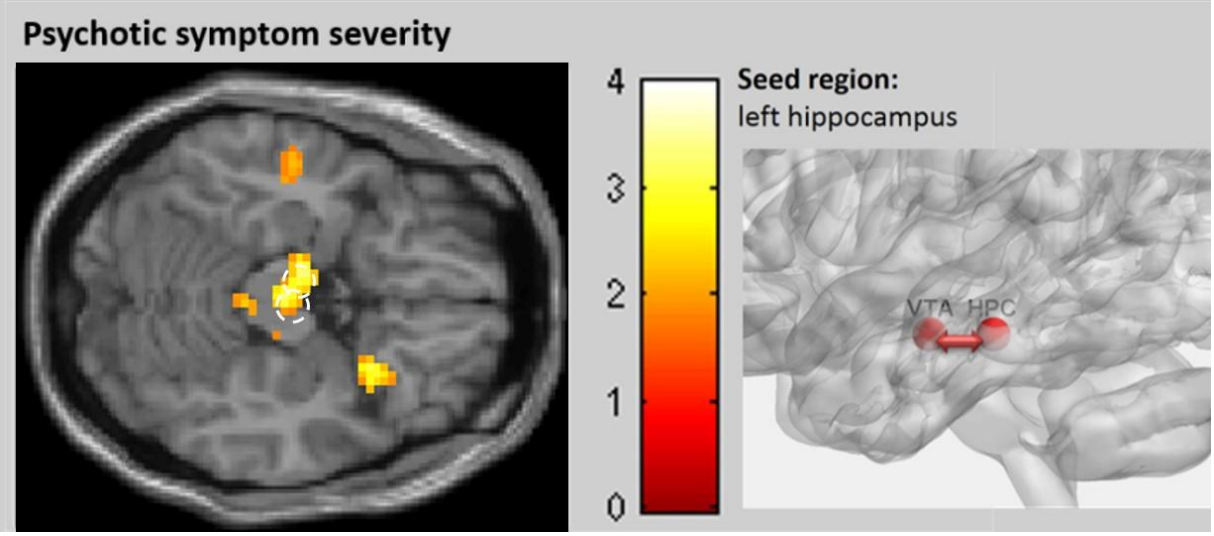


**Figure 6.** Negative correlation of the severity of psychotic symptoms (PANSS psychotic) with the coupling of the left HPC with the VTA/SN (left [-9 -13 -17] t = 3.25, right [3 -19 -14] t = 3.95) during "desire" situations. For illustrational purposes, p level was set at .05, uncorrected. The functional connectivity was visualized with the BrainNet Viewer (http://www.nitrc.org/projects/bnv/) (Xia et al., 2013).

The **right HPC** did not show a significant positive or negative coupling with the vStr or with the VTA/SN, neither in healthy controls nor in SZ patients. Nevertheless, there was a significant group difference concerning the right HPC coupling to the bilateral vStr (left [-6 8 -2] t = 3.01, right [18 8 -8] t = 3.62), which results from a subthreshold negative coupling of the right HPC with both left and right vStr in SZ patients, which was absent in healthy controls. The psychotic symptom severity was not significantly correlated to the right HPC coupling neither with left or right VTA/SN nor with left or right vStr.

Coupling of the left HPC in the desire situation did not significantly correlate with RTs or with error rates during target selection (T-CV10 vs. N-T). Nevertheless, there was a positive correlation of the RT slowing (T-CV10 vs. N-T) and right HPC coupling with the VTA/SN ([-3 -13 -11] t = 3.31). The increase in error rates (T-CV10 vs. N-T) did not significantly correlate with right HPC coupling.

## 2.5 Discussion

The goal of the present study was to investigate the hippocampal functional interaction with the vStr and VTA/SN in SZ patients compared to healthy controls using fMRI. For targeting at these regions, we used an incentive reward paradigm (DRD paradigm) presenting reward stimuli in a context-dependent manner.

Compared to situations in which subjects had to select one stimulus out of two neutral, non-rewarded stimuli, healthy controls and SZ patients showed an increased activation of the bilateral HPC, VTA/SN and vStr, when they could freely select a context-dependent reward stimulus ("desire" situation). Critically, the left vStr activation was abnormally increased in SZ patients. Hyperactivation of the VTA/SN and HPC was also observed but did not reach significance. An additional analysis including the psychotic symptom severity (PANSS psychotic = hallucinations + delusions) as a regressor revealed a significant positive correlation of the severity of psychotic symptoms with HPC and VTA/SN activations. Functional connectivity analyses showed a positive coupling of the left HPC with the left VTA/SN in healthy controls. Critically, this functional connectivity was not observed in SZ patients. For the coupling of the left HPC with left VTA/SN the group comparison did not reach significance. Nevertheless, a post-hoc analysis with psychotic symptom severity as a regressor showed that a lower functional coupling of the left HPC to bilateral VTA/SN was accompanied by increased psychotic symptoms. We did not find a positive coupling of the left HPC with the vStr, neither in healthy controls nor in SZ patients. Instead, there was even a negative coupling in the patient group. Additionally, SZ patients and healthy controls differed regarding their functional connectivity between the right HPC and the bilateral vStr, which was driven by a subthreshold negative coupling in SZ patients that was absent in healthy controls. Behaviorally, the presence of a conditioned reward stimulus during target selection ("desire-reason dilemma" situation) lead to a significant response slowing and a reduced number of correct target selections. Although SZ patients showed an overall significant response slowing and higher error rate, this was not specific for the "desire-reason" dilemma, as interactions of group and task condition did not reach significance. However, the RT slowing was positively correlated with left VTA/SN activation and negatively with right HPC activation. Right HPC coupling with right VTA/SN was positively correlated with RT slowing. Furthermore, there was a positive correlation of increased error rates and right vStr activation.

The hyperactivation of the vStr replicates findings from a previous study by Richter et al. (2015), in which a paradigm with context-independent reward stimuli was used. In contrast,

VTA/SN and HPC hyperactivation failed to reach significance. This was unexpected, as studies with animal models of SZ indicated that a hyperactivated HPC leads to a hyperdopaminergic state (for review see e.g. Grace, 2012, 2016, 2017). As the hippocampal abnormality is thought to underlie the emergence of psychotic symptoms (Grace, 2012), and the variance of symptom severity in our patient sample was relatively high (comprising patients with low, medium and high scores of symptom severity), we performed an additional analysis taking into account the high variance of symptom severity. In this analysis, we only included the patients and used the psychotic symptom severity (PANSS psychotic = hallucinations + delusions) as a regressor. In line with studies showing both structural (e.g. Bogerts et al., 1993; Zierhut et al., 2013) and functional (e.g. Hecker, 2001; Jardri et al., 2011; Lefebvre et al., 2016; Liddle et al., 2000; Schobel et al., 2009) abnormalities of the HPC related to psychotic symptoms, our analysis revealed that HPC activations were positively correlated with the severity of psychotic symptoms. Our finding of a positive correlation of psychotic symptoms and VTA/SN activation is in line with the assumption that psychotic symptoms rely on a DA-dependent process (Belujon & Grace, 2008) and with our prior finding of a hyperactivated dopaminergic midbrain during a combined oddball-incongruence task (Wolter et al., 2016). All in all, these findings suggest that hyperactivation of the HPC may be primarily present in acutely psychotic patients, and not in all patients of our sample. Therefore, in future studies, the inclusion of only acutely psychotic patients may be necessary to find a significant hyperactivation of the HPC in SZ patients compared to healthy controls.

According to findings from animal models, VTA activation is dependent on an activation of the HPC (for review see e.g. Grace et al., 2007; Grace, 2012, 2016). From that perspective, hippocampal and VTA hyperactivation can be expected to be functionally related. In line with that, the left HPC activation showed a positive coupling with the left VTA/SN in healthy controls. Critically, this functional connectivity was absent in SZ patients. While group comparisons again did not reach significance level (probably due to the above-mentioned heterogeneity in symptom severity), a post-hoc analysis with psychotic symptom severity as a regressor showed that a lower functional coupling of the left HPC to bilateral VTA/SN was accompanied by increased psychotic symptoms in the patient group.

Opposed to the findings from rodent studies, as described before, we did not find a positive coupling of the HPC with the vStr, neither in healthy controls nor in SZ patients. Instead, there was even a negative coupling in the patient group. These findings may arise due to our fMRI task-design, which was event-related and therefore able to address phasic neuronal responses

to rewards. In contrast, Grace (2012, 2015, 2016, 2017) describes a modulation of the tonic firing rate of DA neurons in the VTA by the HPC via NAcc, which may be better addressed by a block design. Accordingly, the subthreshold phasic hyperactivation of the VTA/SN, found in our study, may be a secondary consequence of an increased tonic firing rate, as only those spontaneously firing VTA neurons, can be phasically activated in response to a salient stimulus (Grace, 2012, 2015, 2016, 2017).

Using the RT and error rate differences between target selection with and without the presence of a conditioned reward stimulus, we could indirectly examine whether patients were more distracted by the reward stimulus and whether their goal-directed behavior was more disrupted by the reward stimulus. A higher behavioral disruption would be in line with the increased bottom-up activity and decreased top-down regulation of reward-related activity in the vStr observed in SZ (Richter et al., 2015). However, we could not find a significant difference in RT or error rate specific for the "desire-reason" dilemma. To directly address this aspect of higher distractibility by conditioned reward stimuli, future studies should use eye-tracking. However, higher distractibility in terms of slower RTs was shown to be related to VTA/SN neuron activation. Accordingly, aberrant VTA/SN activation was found in SZ patients in a combined oddball-incongruence task, in which relevant processing must be shielded from distracting irrelevant salient or conflicting information (Wolter et al., 2016).

One limitation of the present study is the already described heterogeneity of our patient sample. Future studies should restrict the patient sample to be either acutely psychotic or remitted to find group differences even at a significance level correcting for multiple comparisons. Our correlational analyses already indicate the relevance of current symptom status during time of fMRI measurement, although these findings have to be proven with a more appropriate study design (with a bigger sample size) to investigate subgroups of SZ patients.

Further research is necessary to determine, whether the hyperactivation of the HPC is related to the presence of psychotic symptoms only in SZ or also in other disorders, like unipolar and bipolar depression and which effect (antipsychotic) medication has on that hyperactivation. In the future, longitudinal studies may give us more information about the sequential development of different pathophysiological changes in SZ and help us to better understand the pathophysiological changes during the course of illness.

In conclusion, hyperactivation of the HPC during dopaminergic reward processing and a disrupted functional coupling of the HPC and the VTA/SN seem to be important pathophysiological mechanism underlying psychosis in SZ patients. To our knowledge, this is

the first neuroimaging study in humans showing both psychosis-related HPC activation and activation of the dopaminergic midbrain (VTA/SN), thereby linking hippocampal abnormalities to the hyperdopaminergic state in SZ.

# 3 Pathophysiological changes of neurofunctional interaction between the dopaminergic reward system and the hippocampus in bipolar disorder

## 3.1 Abstract

Abnormalities of the dopaminergic reward system and of the HPC have been shown to play a major role for both SZ and BD. A direct link between both abnormalities has been shown in both an animal model for SZ and in the previously described human fMRI study with SZ patients using the DRD paradigm with context-dependent reward stimuli. This link has not been hypothesized for the pathophysiology of BD so far. Nevertheless, both disorders show a large genotype and phenotype overlap suggesting that the neurofunctional interaction of the HPC and the dopaminergic reward system may also be relevant for patients with BD. To elucidate the neurofunctional interaction of the HPC, the VTA and the vStr in BD patients, the above-mentioned paradigm was used in the current fMRI study to compare 20 BD patients and 20 healthy controls matched for age, sex and education. BD patients showed an abnormal reward-related functional connectivity between HPC and VTA/SN. Thereby, this study provides first evidence for a neurofunctional link between abnormalities of HPC and the dopaminergic reward system in BD. Accordingly, an abnormal functional connectivity between HPC and VTA/SN could also be shown in SZ, thereby this study reveals a neurofunctional overlap of both disorders.

## 3.2 Introduction

A dysregulation of the dopaminergic reward system has been hypothesized to be involved in the pathophysiology of SZ (Davis et al., 1991; Howes & Kapur, 2009) and affective psychoses (Ashok et al., 2017; Singh, 1970; Tissot, 1975; Wittenborn, 1974) and seems to be implicated in both psychotic and mood symptoms of psychoses. Although the BD is mainly characterized by mood symptoms, both manic/hypomanic and depressive episodes can be accompanied by psychotic symptoms (e.g. delusions and hallucinations), which are core symptoms of SZ (WHO, 1993). While a (striatal) hyperdopaminergic state for SZ is assumed (Davis et al., 1991), the dysregulation of the dopaminergic system in BD seems to be more complex. According to the dopamine hypothesis of the disorder, manic episodes are characterized by

hyperdopaminergia, whereas depressive episodes are characterized by hypodopaminergia (Ashok et al., 2017).

DA neurotransmission is important for numerous cognitive and emotional processes, but has mainly been implicated in reward processing (Haber, 2014). The vStr, the core region of dopaminergic reward system, receives dopaminergic input from the VTA, and is activated both in response to and in anticipation of reward. The dopaminergic reward system receives modulatory input from the cortex, particularly from the frontal cortex, and from limbic regions, like the HPC (Haber & Knutson, 2010; Haber 2014; Robbins & Everitt, 1996; Sesack & Grace, 2010).

Dysfunctions of the dopaminergic reward system have been shown in BD patients during anticipation of reward (Caseras et al., 2013; Mason et al., 2014; Nusslock et al., 2012) as well as during reward feedback (Abler et al., 2008; Caseras et al., 2013; Dutra et al., 2015; Mason et al., 2014; Redlich et al., 2015; Trost et al., 2014). The findings are partially conflicting, ranging from hyperactivation (Caseras, et al., 2013; Dutra et al., 2015; Mason et al., 2014; Nusslock et al., 2012) to hypoactivation (Abler et al., 2008; Trost et al., 2014; Redlich et al., 2015) and studies showing no differences between patients and healthy controls (Bermpohl et al., 2010; Chase et al., 2013; Linke et al., 2012; Satterthwaite et al., 2015; Singh et al., 2013; Yip et al., 2015). These heterogenous findings seem to arise mainly from two factors. First, much of the divergence may be due to differing sample characteristics. In euthymic phase of illness, the vStr seems to be hyperactivated during anticipation of reward both in bipolar I (Nusslock et al., 2012) and bipolar II (Caseras et al., 2013; Mason et al., 2014) patients. Although there are also studies showing no difference between patients and controls (Dutra et al., 2015). Second, results seemed to be dependent on whether reward anticipation or feedback was investigated. For example, Abler and colleagues (2008) found a decreased vStr activation in manic BD patients during reward feedback but not during anticipation. Mason et al. (2014) found an increased vStr activation in euthymic BD patients during reward anticipation but not during reward feedback, whereas Dutra (2015) reported contrasting results. Caseras et al. (2013) reported a hyperactivation of the vStr in euthymic BD I patients during reward anticipation and in euthymic BD II patients during reward feedback.

Beside this, there are also studies reporting abnormal functional connectivity of the dopaminergic reward system with other regions of the brain. In a study of Trost and colleagues (2014), they could not only show a decreased activation of the vStr, but also a decreased suppression of the vStr during situations, in which subjects had to reject an immediate reward

stimulus in favor of achieving the long-term goal of the task. This was accompanied by an abnormal functional coupling of the ventral striatum with anteroventral prefrontal cortex.

Another important source of regulatory input to the VTA and vStr is the HPC. The functional role of this hippocampal input seems to be the modulation of the stimulus-elicited activity in the VTA dependent on the behavioral context (Grace, 2010a, b, 2012, 2016). In a previously described study (see chapter 2), we could show that the HPC is coactivated with the VTA and vStr during the presentation of context-dependent reward stimuli. The HPC and the VTA/SN of SZ patients seems to be hyperactivated in response to those stimuli, dependent on their psychotic symptom severity. This finding is in line with evidence from an animal model of SZ, in which hyperactivation of the HPC leads to a hyperdopaminergic state and psychotic-like behavior (Lodge & Grace, 2007). Furthermore, SZ patients have been shown to display an abnormal functional connectivity of the HPC with the VTA/SN and vStr (see chapter 2.4.2).

Although there are also neuroimaging studies, showing abnormal activation of the HPC and other limbic and paralimbic brain regions in BD (Blond et al., 2012; Brambilla et al., 2008; Chen et al., 2011; Femenía et al., 2012; Glahn et al., 2010; Lagopoulos & Malhi, 2007; Malhi et al., 2007; Pavuluri et al., 2007; Whalley et al., 2009), evidence how this dysfunction relates to the patients' DA abnormalities, is still missing. Nevertheless, it has been suggested by Phillips et al. (2003) that a hippocampal dysfunction is related to an increased sensitivity for the identification of emotionally salient environmental information thereby leading to contextually inappropriate affective states. So far, the role of the HPC has only been tested for the processing of emotionally salient information but not for reward-related stimuli.

In a prior study with euthymic to mildly depressed BD patients, a hyposensitivity for reward-stimuli has been shown for the vStr (Trost et al., 2014). Whether this abnormality is related to an abnormal HPC activation or connectivity, remains to be elucidated. To investigate the HPC' activation and connectivity with the dopaminergic reward system in patients with BD, we used a modified version of the classical DRD-paradigm with context-dependent reward stimuli that has already been used in the previously described study with SZ patients (chapter 2).

## 3.3 Methods

### 3.3.1 Subjects

20 patients with BD and 20 healthy controls – matched for sex, age and education – were included in the analyses. Patients and healthy subjects were excluded from participation in cases of current drug abuse, current or anamnestic substance-related addiction and neurological disease. Furthermore, subjects with extensive head motion (>4mm) during scanning were excluded from the analyses.

Patients were recruited from inpatient and outpatient settings of the Department of Psychiatry and Psychotherapy, University Medical Center Göttingen. Their diagnoses were consented with the treating psychiatrists.

The symptom severity was assessed one day before scanning with the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979), the Young Mania Rating Scale (YMRS; Young et al., 1978), the Beck Depression Inventar (BDI II; Beck et al., 1996) and the Clinical Global Impression Scale (CGI; Guy, 1976). According to the CGI severeness scale, 14 BD patients have been rated as mildly ill, four patients as moderately ill, and two patients as markedly ill. Based on the BDI II score, nine patients fulfilled criteria for minimal depression (score 0-13), 1 patient fulfilled criteria for mild depression (score 14-19), four patients fulfilled criteria for moderate depression (score 20-28) and six patients fulfilled criteria for severe depression (score 29-63). Regarding manic symptoms, none of the patients fulfilled criteria for mania (score >12). Detailed sample characteristics can be seen in table 3.

### 3.3.2 Experimental protocol

During fMRI scanning subjects performed a modified version of the "desire-reason dilemma" (DRD) paradigm. In this task, depending on the situation, subjects must accept or reject a previously conditioned reward stimulus. Those trial conditions have previously been shown to be suitable to evoke bottom-up activation and top-down suppression of vStr, respectively (Diekhof & Gruber, 2010; Diekhof et al., 2012a; Diekhof et al., 2012b; Goya-Maldonado et al., 2015; Richter et al., 2015; Trost et al., 2014; Trost et al., 2016; Wolf et al., 2016).

One day before scanning, subjects performed a conditioning task outside the scanner, in which, depending on the background photograph, selection of some stimuli is rewarded with ten points. The details of the conditioning procedure have already been described in chapter 2.3.2.

**Table 3.** Demographical and clinical characteristics of the subjects.

| | | | Bipolar patients | Healthy controls | *p* value |
|---|---|---|---|---|---|
| Sample size | | | 20 | 20 | |
| Gender (% female) | | | 55.0 | 50.0 | .76[b] |
| Handedness (% left handed) | | | 10.0 | 0.0 | .15[b] |
| Age at time of testing (in years) | | | 38.3 ± 11.3 | 32.45 ± 12.2 | .12 |
| Education (in years) | | | 14.9 ± 2.6 | 15.1 ± 2.7 | .86 |
| MWT-A | | | 31.0 ± 3.4 | 31.6 ± 1.5 | .48 |
| BDI II | | | 17.7 ± 13.3 | 4.0 ± 6.4 | .00* |
| MADRS | | | 11.5 ± 11.3 | | |
| YMRS | | | 4.5 ± 4.6 | | |
| CGI | | | 3.4 ± .7 | | |
| Age of onset (years) | | | 24.8 ± 10.2 | | |
| Duration of illness (years) | | | 6.2 ± 4.7 | | |
| Medication (absolute frequency) | Neuroleptics | Atypical neuroleptics | 12 | | |
| | | Atypical and typical neuroleptics | 1 | | |
| | Anti-depressants | SSRI | 5 | | |
| | | SSNRI | 1 | | |
| | | SNDRI | 2 | | |
| | | Tricyclics | 1 | | |
| | Mood stabilizer (Lithium) | | 10 | | |
| | Benzodiazepine | | 2 | | |
| | β-blockers | | 1 | | |
| | Anticonvulsives | | 10 | | |

*Abbreviations:* BDI, Beck Depression Inventar; CGI, Clinical Global Impression Scale; MADRS, Montgomery-Åsberg Depression Rating Scale (MADRS); MWT-A, Mehrfachwahl-Wortschatz Intelligenztest (multiple-choice vocabulary intelligence test); SNDRI, Selective Noradrenaline-Dopamine Reuptake Inhibitors; SSNRI, Selective Serotonin-Norepinephrine Reuptake Inhibitors; SSRI, Selective Serotonin Reuptake Inhibitor; YMRS, Young Mania Rating Scale. * significant group difference ($p < .05$) [a] *P* values for group differences determined by the non-parametrical Mann-Whitney test.

Unless otherwise indicated: Data are presented as mean ± standard deviation. *P* values for group differences were determined by an independent samples t-test (two-sided).

In the actual task during scanning, subjects had to select one out of two simultaneously presented colored stimuli. However, in this task a target stimulus was introduced at the beginning of each block of eight trials. This stimulus had to be chosen, if present, during the subsequent trials. Subjects were informed that they would get 60 points at the end of the block for collecting all the targets present in the respective trials and that missing one of the targets causes a loss of all target points. Additionally, subjects could get ten bonus points for collecting the stimuli, which were rewarded during the previous conditioning task. Again, the rewarding of those stimuli depended on the context, which could vary from block to block. Furthermore, subjects were informed that the points collected during scanning would be afterwards transferred to money (up to 30 €). Subjects practiced the task one day before and immediately before scanning. The training procedure and the timing of the task was already described in chapter 2.3.2.

Pairings of a bonus stimulus with a non-target (N-CV10) constituted the "desire situation", as the bonus stimulus could be freely chosen. Contrary to this, in the "desire-reason dilemma" the conditioned stimulus was paired with a target stimulus (T-CV10). Selecting the "desired" bonus stimulus was not reasonable in this situation, as the subject would have lost all the target points. Whereas, the desire situation can be used to investigate bottom-up activation of the reward system, the desire-reason dilemma has shown to be an appropriate condition for the investigation of (top-)down-regulation of the reward system, especially of the vStr, by the avPFC (Diekhof & Gruber, 2010; Diekhof et al., 2012a, 2012b; Goya-Maldonado et al., 2015; Richter et al., 2015; Trost et al., 2014; Trost et al., 2016; Wolf et al., 2016). As bonus stimuli were also presented in front of the context, in which they were not rewarded, a "pseudo-desire situation" (N-CV0) and a "pseudo-desire-reason dilemma" (T-CV0) could arise, when those stimuli were paired with non-targets or targets, respectively. Pairings of a non-target with another non-target (N-N) served as a control condition for the "desire situation", whereas pairings of a target and non-target (N-T) served as a control condition for the "desire-reason dilemma". The positions of the six possible stimulus pairs with the blocks and their transitions from trial to trial were counterbalanced, whereby each stimulus type was presented equally often at the left and at the right side.

### 3.3.3 fMRI acquisition

A total of 825 volumes was acquired in three functional runs using an echo planar imaging (EPI) sequence (interscan interval (TR): 1,800 ms; echo time (TE): 30 ms; flip angle: 70°) with an 8-channel head coil in a 3T Siemens TRIO MRI scanner (Siemens Healthcare, Erlangen,

Germany). 34 axial slices parallel to the anterior commissure-posterior commissure line were obtained in ascending acquisition order (voxel size: 3x3x3 $mm^3$, interslice gap: 20 %) using a gradient-echo echo-planar imaging (EPI) sequence (field of view: 192 mm, matrix size: 64x64). Stimuli were presented via goggles and subjects responded via button press on a fiber optic computer response device. Stimulus delivering and synchronization with scanner was conducted through the Presentation® Software (Neurobehavioral Systems, Albany).

### 3.3.4 Behavioral data analysis

The behavioral data were analyzed using IBM SPSS statistics for Windows, version 24 (SPSS Inc., Chicago, IL). Mean RTs and error rates have been defined at single-subject level. To calculate the effect of the presence of a bonus stimulus on goal-directed behavior during target selection, we compared RTs and error rates of "desire-reason dilemma" situations (T-CV10) with RTs and error rates in trials with targets that were paired with non-targets (N-T).

RTs and error rates were analyzed using a mixed 2*2 ANOVA model with task condition (N-T, T-CV10) as a within-subject factor and group (healthy controls, SZ patients) as a between-subject factor. Only RTs of correct trials were included in the analysis, whereby errors were defined as choosing the non-target or bonus-stimulus in presence of a target, or giving no response at all (omissions). All tests were thresholded at $p < .05$, two-sided.

### 3.3.5 fMRI data analysis

Preprocessing and statistical analyses of functional data were performed using SPM8 (Wellcome Department of Imaging Neuroscience, London, UK). Preprocessing comprised realignment and unwarping, correction for slicetime acquisition differences (reference slice: 1) and low frequency fluctuations, normalization into standard stereotactic space (to the Montreal Neurological Institute (MNI) skull-stripped structural template), and spatial smoothing with a Gaussian kernel of 8 mm FWHM.

For the 1st level statistical analysis of the functional images, the onsets of the experimental conditions were modelled by the convolution with a hemodynamic response function accounting for the delay of the BOLD (blood oxygen level-dependent) response. For each subject, statistical images were computed for each condition against an implicit baseline.

For the 2nd level statistical analysis, these first-level images were included in an ANOVA with group (BD patients, healthy controls) and task condition (N-N, N-T, N-CV0, N-CV10, T-CV0, T-CV10) as a within-subject factor. Effects of the conditions were then calculated for each group separately using t-contrasts. We compared the brain activation during the "desire

situations" with brain activation during trials with only neutral stimuli (N-N), to extract activation related to reward-processing. Group comparisons of the statistical images were calculated using t-contrasts. To assess the correlation of symptom severity (e.g. MADRS, YMRS, BDI II, CGI scores) and activation of the vStr, the VTA/SN and the HPC/subiculum, the patients` symptom scores were used as covariates of interest in additional one-sample t-tests.

To elucidate the functional interaction of the HPC and both the VTA/SN and the vStr, we calculated psycho-physiological interactions (PPIs) using spheres (radius 3 mm) around coordinates from schizophrenia patients of the first study as seed regions.

Due to our a priori anatomical hypotheses, we used the small-volume corrected p-value ($p < .05$) as a statistical threshold. Regions of interest were defined using boxes (12x12x12 $mm^3$) around vStr and VTA coordinates from Diekhof and Gruber (2010) and using anatomical masks for the left and right subiculum created by the SPM Anatomy Toolbox (version 2.0).

## 3.4 Results

### 3.4.1 Behavioral data

For RTs, both main effects reached the significance level (task condition $F(1,38) = 30.531$, $p < .001$, $\eta^2 = .446$; group $F(1,38) = 6.944$, $p < .05$, $\eta^2 = .155$). The interaction effect was not significant. The main effect of task condition was driven by a relative RT slowing during target selection when a reward stimulus was present, while the main effect of group was driven by a relatively slower RT in the BD group compared to healthy controls. Within-group comparisons revealed a significant RT difference between task conditions in healthy controls ($p < .001$), and BD patients ($p < .01$) (see figure 7).

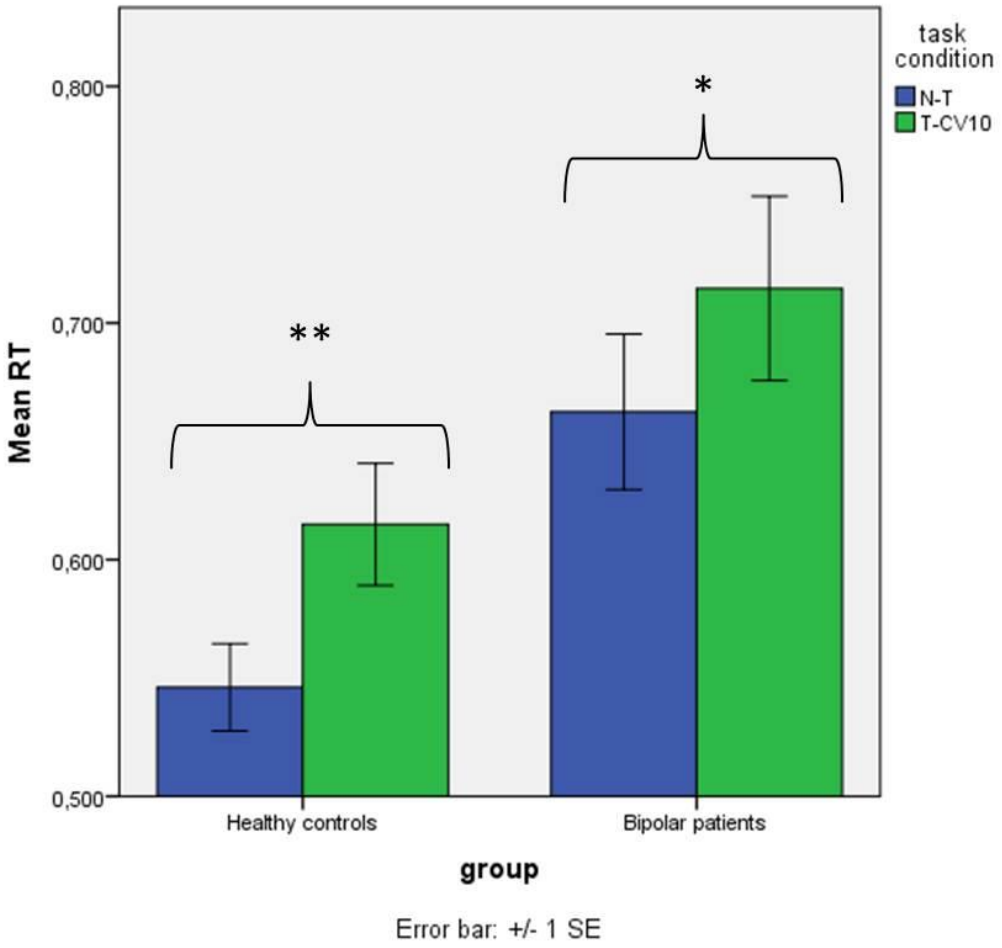


**Figure 7.** Mean reaction time (RT) of healthy controls and bipolar patients (± standard error (SE)). The RT in trials with targets paired with a conditioned reward stimulus (T-CV10) was significantly increased compared to trials with targets paired with a non-target (N-T) in healthy controls and bipolar patients. ** $p < .001$; * $p < .01$.

For error rates, again, only the main effect of task condition reached the significance level ($F(1,38) = 22.653$, $p < .001$, $\eta 2 = .373$). Contrary, neither the main effect of group nor interaction effect were significant. The main effect of task condition was driven by a higher error rate during target selection when a reward stimulus was present. Within-group comparisons revealed a significant error rate difference between task conditions in healthy controls ($p < .005$) and BD patients ($p < .001$) (see figure 8).

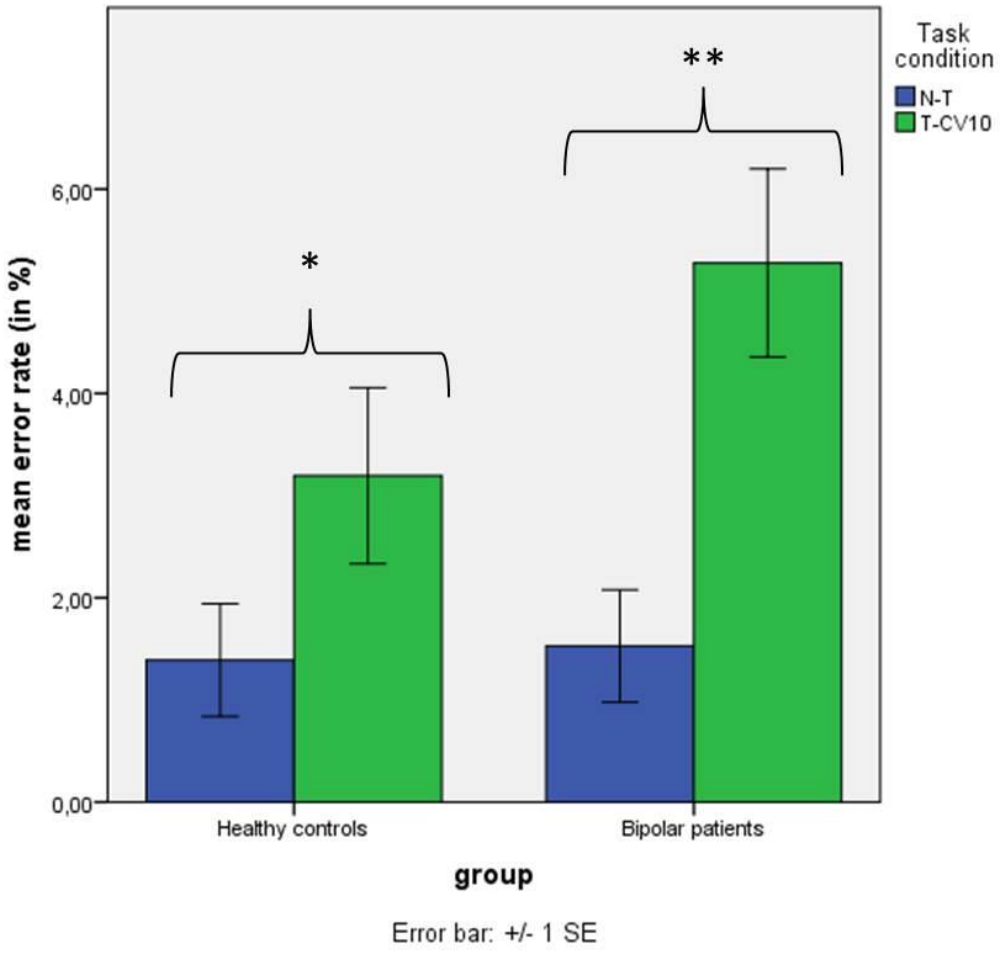


**Figure 8.** Mean error rate of healthy controls and bipolar patients (± standard error (SE)). The error rate in trials with targets paired with a conditioned reward stimulus (T-CV10) was significantly increased compared to trials with targets paired with a non-target (N-T) in healthy controls and bipolar patients. ** $p < .001$; * $p < .005$.

### 3.4.2 fMRI data

During the "desire situation" all ROIs (VTA, vStr and HPC) were significantly activated (see table 4, for whole-brain results see Supplement Table S2). Both healthy controls and BD patients showed an activation of the bilateral HPC, the bilateral VTA/SN and the bilateral vStr.

Group comparisons did not reach significance, although there was a subthreshold hypoactivation of the right vStr, replicating findings of a previous study (Trost et al., 2014) (see table 4). Furthermore, there was a subthreshold hypoactivation of right HPC and a subthreshold hyperactivation of the bilateral VTA/SN and left HPC. Activation neither of the vStr nor of the VTA/SN or HPC were significantly correlated with the severity of depressive symptoms.

**Table 4** Reward-related brain activations in the "desire context" in bipolar patients compared to healthy controls

| **Region** | **Bipolar patients** | **Healthy controls** | **Bipolar patients > Healthy controls** | **Healthy controls > Bipolar patients** |
|---|---|---|---|---|
| | MNI coordinates (*t*-values) | MNI coordinates (*t*-values) | MNI coordinates (*t*-values) | MNI coordinates (*t*-values) |
| L vStr | -18 5 1 (3.28) | -9 11 -5 (4.84) | n.s. | n.s. |
| | *-15 2 7 (3.90)* | | | |
| R vStr | n.s. | 12 8 -2 (5.09) | n.s. | [9 11 -8 (2.29)] |
| L VTA/SN | -9 -25 -17 (4.18) | -15 -22 -11 (3.69) | [-3 -25 -14 (2.25)] | n.s. |
| | *-18 -34 -17 (4.76)* | | | |
| R VTA/SN | 15 -25 -23 (3.97) | 15 -22 -11 (3.76) | [12 -13 -23 (2.21)] | n.s. |
| | | *21 -22 -11 (4.37)* | [3 -25 -14 (2.11)] | |
| L HPC | -18 -34 -14 (4.56) | -24 -28 -14 (3.86) | [-15 -31 -14 (1.89)] | n.s. |
| | *-18 -34 -17 (4.76)* | | *[-15 -34 -23 (2.26)]* | |
| R HPC | 24 -31 -17 (3.48) | 21 -31 -8 (4.63) | n.s. | [21 -31 -8 (1.78)] |
| | *27 -34 -26 (4.10)* | *18 -28 -8 (4.67)* | | |

*Abbreviations:* HPC, hippocampus; L, left; MNI, Montreal Neurological Institute; n.s., not significant; R, right; SN, substantia nigra; vStr, ventral striatum; VTA, ventral tegmental area.

If not indicated differentially, effects on regional brain activation were significant at a level of $p < .05$, FWE-corrected for the small volume. Local maxima outside the defined ROI are reported italicized. * Brain activations, which are additionally significant at a level of $p < .05$, FDR-corrected for whole brain. For purposes of completeness and better understanding, subthreshold effects ($p < .05$, uncorrected) are reported using square brackets.

In healthy controls, left HPC did not show a significant functional connectivity with the VTA/SN, although they showed a subthreshold positive coupling of left HPC with the right vStr and the bilateral VTA/SN. In contrast, BD patients showed a significant negative coupling of the left HPC with the right vStr ([9 8 -11] t = 3.53), and at a subthreshold level with left vStr and bilateral VTA/SN.

Group comparisons revealed a significantly reduced coupling of the left HPC and the left VTA/SN in BD patients compared to healthy controls ([-3 -16 -20] t = 3.24) (see figure 9).

Functional connectivity of the left HPC with the VTA/SN and vStr was not significantly correlated with depressive symptom severity (BDI II score).

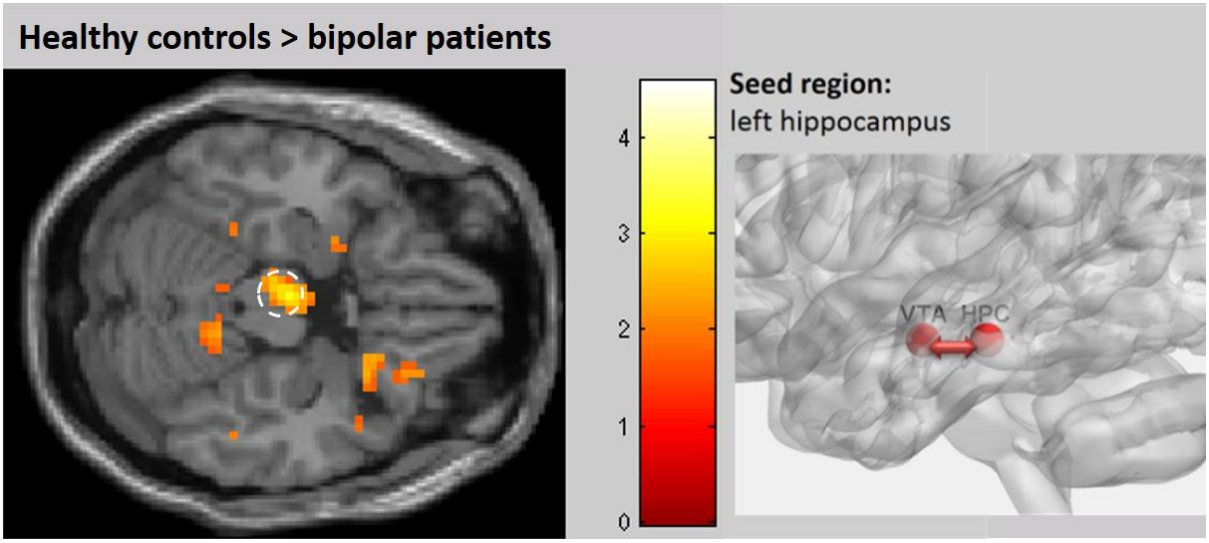


**Figure 9.** Reduced functional connectivity of the left hippocampus and the left ventral tegmental area/substantia nigra in bipolar patients compared to healthy controls ([-3 -16 -20] t = 3.24). For illustrational purposes, p level was set at .05, uncorrected. The functional connectivity (right image) was visualized with the BrainNet Viewer (http://www.nitrc.org/projects/bnv/) (Xia et al., 2013).

The right HPC did show a significant positive coupling with the left VTA/SN ([-12 -16 -14] t = 3.95) and at a subthreshold level with the left vStr and bilateral VTA/SN in healthy controls. In BD patients neither vStr nor VTA/SN showed a significant coupling with the right HPC, although there was a subthreshold positive coupling of the right HPC with the left vStr and subthreshold negative coupling with the right vStr. Group differences did not reach significance. Nevertheless, there was a significant negative correlation of the depressive symptom severity (BDI II score) and the coupling between right HPC and right vStr ([18 5 1] t = 3.81).

### 3.4.3 Comparison to schizophrenia patients

RT slowing and error rate increase (T-CV10 vs. N-T) were compared between BD and SZ patients using two-sample t-tests. These analyses did not reveal a significant difference between both patient groups neither for RTs nor for error rates.

To compare the reward-related activation and connectivity between BP and SZ patients, first-level images were included in a two-sample t-test. Neither activity nor connectivity did significantly differ between groups.

## 3.5 Discussion

The goal of the present study was, on the one hand, to examine reward-related functional activation and connectivity of HPC, VTA/SN and vStr in BD patients compared to healthy controls using fMRI with context-dependent reward stimuli and on the other hand, to compare abnormalities of functional activation and connectivity to the abnormalities previously found in SZ patients. Although both groups showed a significant reward-related activation of all the ROIs, patients showed a subthreshold hypoactivation of the right vStr and right HPC as well as a subthreshold hyperactivation of the bilateral VTA/SN and left HPC. Furthermore, we found an abnormal functional coupling of the left HPC and the left VTA/SN. The coupling of the right HPC did not differ significantly between groups, although there was a significant negative correlation of the depressive symptom severity and the coupling between right HPC and right vStr. BD patients and SZ patients did not differ significantly in activation or connectivity and did not show a difference in RT slowing and error rate increase, when targets were paired with a conditioned reward stimulus ("dilemma" situation) compared to trials in which targets were paired with a non-target (N-T).

The finding of an activation of the VTA/SN and the vStr during the presentation of reward-related stimuli is replicating previous findings (Diekhof & Gruber, 2010; Diekhof et al., 2012a, 2012b; Goya-Maldonado et al., 2015; Richter et al., 2015; Trost et al., 2014; Trost et al., 2016; Wolf et al., 2016). The attended coactivation of the HPC with the dopaminergic reward system was successful and is replicating results of the previously described study with SZ patients, when context-dependent reward stimuli were used (see chapter 2). Replicating the findings from Trost et al. (2014), activation of the vStr was reduced in BD patients compared to healthy controls, although the hypoactivation in the current study was present only at a subthreshold level. Although hypoactivation of the vStr and other regions of the dopaminergic reward system has been previously found in BD patients in studies using other reward paradigms (Abler et al., 2008; Redlich et al., 2015), some studies did found a hyperactivation (Caseras et al., 2013; Dutra et al., 2015; Mason et al., 2014; Nusslock et al., 2012), while other did not find significant differences between BD patients and healthy controls (Bermpohl et al., 2010; Chase et al., 2013; Linke et al., 2012; Singh et al., 2013; Satterthwaite et al., 2015; Yip et al., 2015). The partly conflicting findings could possibly result from different sample characteristics, like illness phase and symptom severity. While Trost and colleagues (2014) included euthymic to mildly depressed patients, the sample of the current study was more heterogenic, including patients with minimal to severe depression. The depressive symptom severity was not related to vStr

activation. All in all, these findings indicate that vStr hypoactivation may be state-independent and may therefore constitute a possible endophenotype marker of bipolar disorder. As assumed in the dopamine hypothesis of BD, depressive episodes are characterized by a hypodopaminergic state, whereas manic episodes are characterized by hyperdopaminergia (Ashok et al., 2017). In so far, our results are in line with the first part of the hypothesis, while we cannot draw any conclusions about the second part of the hypothesis as our sample did not include patients with current mania. Regarding the vStr activation, BD patients and SZ patients seem to display an opposite direction of abnormality, with a hyperactivation in SZ patients and a hypoactivation in BD patients, nevertheless the direct comparison of both groups did not show significant differences.

In our study with SZ patients, hippocampal activation was increased at a subthreshold level, compared to the activation of healthy controls, and was significantly related to psychotic symptom severity. In BD, we could also find a subthreshold hyperactivation. Critically, our BD sample did not show relevant psychotic symptoms. It remains to be elucidated, whether activation of the HPC is also related to psychotic symptoms in BD patients. This would be in line with the hypothesis, that hyperactivation of the HPC may be inherent to psychosis in general rather than psychosis specific to SZ (Howes & Kapur, 2009).

Interestingly, BD patients showed an abnormal functional connectivity of the left HPC with the left VTA/SN. This abnormality seems to be similar to the abnormality seen related to psychosis in SZ patients, pointing to a shared pathophysiological mechanism of both disorders. This is, to our knowledge, the first study showing an abnormal functional connectivity of the HPC and the VTA/SN. Although there has already been a study showing a paucity of normal inter-relations of the HPC with other brain regions in BD disorder (Benson et al., 2014). Moreover, there is also a study reporting cross-disorder similarities in hippocampal resting-state connectivity abnormalities with other brain regions in SZ patients, patients with schizoaffective disorder and psychotic BD (Samudra et al., 2015).

Another interesting finding of the current study is the negative correlation of depressive symptom severity and the functional connectivity of the right HPC with the right vStr. More specifically, a higher severity of depressive symptoms was associated with a reduced positive connectivity of the right HPC with the right vStr. To our knowledge, this is the first neuroimaging study relating depressive symptoms to an abnormal HPC-vStr connectivity. Nevertheless, in the learned helplessness animal model of depression, helpless animal's tetanic stimulation of the HPC–NAcc pathway has been shown to induce long-term depression,

whereas control rats and non-helpless rats show long-term potentiation (Belujon & Grace, 2014; Grace, 2016).

Critically, from our analyses we cannot draw any conclusions about the direction of the functional connectivity of the HPC and the VTA/SN or the HPC and the vStr. So, we do not know which kind of information flow is disrupted in BD – the input to or the output from the HPC. Although the abnormal functional connectivity of the HPC in BD patients is pointing to the same direction as in SZ patients, we do not know, whether it represents the same pathophysiological mechanism. Future studies should try to disentangle state and trait-related abnormalities in BD and compare depressive, euthymic and manic patients.

All in all, our results again highlight the relevance of the dopaminergic reward system for BD. Furthermore, this study extends the previous view of the dopaminergic system as a singular disrupted system in this disorder to broader view of abnormal interactions between the DA system and other systems like the mainly glutamatergic HPC.

# 4 General discussion

## 4.1 Summary of the results

In a translational and transdiagnostic framework, this thesis aimed to investigate a set of brain regions in SZ and in BD, which were previously shown by neurophysiological studies in animals to functionally interact with each other and to be relevant for both psychiatric disorders. This set of brain regions included the vStr, the VTA/SN and the HPC.

Hyperactivation of the vStr in SZ (Richter et al., 2015) and hypoactivation of the vStr in BD (Trost et al., 2014) were findings of previous studies using the DRD paradigm to investigate the dopaminergic reward system. Using a modified version of this paradigm with context-dependent reward stimuli we could replicate these prior results.

Due to the context-dependence of the reward stimuli in this new paradigm, we were able to examine activation of the HPC. In a yet unpublished study with healthy controls, the HPC was shown to be co-activated with other reward-related brain regions when the rewarding of the stimuli was dependent on the context. One major finding of this thesis is that the severity of psychotic symptoms in SZ patients was significantly related to the HPC activation – with a tendency of an increased activation of the HPC in SZ patients compared to healthy controls. In BD patients, there was also a subthreshold hyperactivation of the HPC, while there was no significant correlation of HPC activation with depressive symptom severity.

Additional functional connectivity analyses revealed an abnormal coupling between the left HPC and the left VTA/SN in both SZ and BD patients, pointing to a shared pathophysiological mechanism of both disorders. This abnormality was found to be related to the psychotic symptom severity in SZ patients, but not to the depressive symptom severity in BD patients. The functional coupling of the right HPC with bilateral vStr was significantly reduced in SZ patients, independent of psychosis severity. Nevertheless, the abnormal functional connectivity of the right HPC and the right vStr was significantly related to depressive symptoms in BD.

Behaviorally, we wanted to examine whether our findings regarding functional abnormalities of our ROIs have a behavioral correlate. More specifically, we wanted to show the behavioral impact of higher brain activation in response to conditioned reward-stimuli. The behavioral impact of the presence of a conditioned reward-stimulus can be well observed in the "desire-reason dilemma" situation of the DRD paradigm. In this situation, the immediately rewarded stimulus must be rejected and a target stimulus has to be selected to achieve the superordinate

goal of the task. Compared to situations in which the target is paired with a neutral non-target the decision has been shown to be significantly slower in "dilemma" situations. Furthermore, subjects more often failed to select the target in "dilemma" situations. The impact of conditioned reward stimuli on proper target selection was not significantly increased in SZ or BD patients. Nevertheless, left VTA/SN and right vStr activation were positively related to a higher impact of conditioned reward stimuli on proper target selection. In contrast, higher right HPC activation was related to a lower impact of conditioned reward stimuli on proper target selection.

In line with the transdiagnostic framework of this thesis, we wanted to know whether there are significant differences between SZ and BD patients. Significant differences have not been found between BD and SZ patients, neither regarding behavior nor regarding brain activation or connectivity.

## 4.2 Translating findings in animal studies to the clinic setting

In the MAM animal model of SZ, hippocampal dysfunction is induced via injection of MAM acetate during pregnancy. This leads to SZ-like behavior and physiological changes in the adult offspring of these rats, which are typically observed in SZ patients (Grace, 2010a, b, 2012, 2015, 2016, 2017). In addition, these rats showed a hyperactivation of the ventral HPC. This hyperactivation has been shown to lead to an increased spontaneous firing in VTA neurons (Lodge & Grace, 2007). As only spontaneously firing VTA neurons, can be phasically activated by a salient event (Floresco et al., 2003; Lodge & Grace, 2006), hippocampal activity is assumed to indirectly increase the gain of the phasic VTA signal in response to salient stimuli.

The DRD paradigm is a flexible paradigm, which can be used to investigate the dopaminergic reward system and its regulation in both healthy subjects and different patient populations. It uses conditioned reward stimuli to activate the dopaminergic system of the brain. Reward stimuli are salient stimuli which are thought to elicit at phasic response in the VTA and the vStr of the brain (Haber & Knutson, 2010). Accordingly, multiple studies using this paradigm found a significant activation in the areas of the VTA and the vStr during presentation of conditioned reward stimuli (Diekhof & Gruber, 2010; Diekhof et al., 2012a; Diekhof et al., 2012b; Goya-Maldonado et al., 2015; Richter et al., 2015; Trost et al., 2014; Trost et al., 2016; Wolf et al., 2016). This could be replicated in the two studies of this thesis, even with a modification of this

paradigm. Furthermore, as we used context-dependent reward stimuli in this modification, the HPC could be co-activated.

Based on findings from MAM model of SZ, we expected to see an increased response of the VTA to salient reward stimuli in SZ patients compared to healthy controls. Due to the context-dependency of the reward stimuli in the projects of the present thesis and prior findings in healthy controls, we expected that the increased activation of the VTA should be accompanied by an increased activation of the HPC and furthermore of the NAcc to which the HPC projects. Reward-related NAcc hyperactivation has already been shown in a previous study of our group using the DRD paradigm (Richter et al., 2015).

Replicating previous results (Richter et al., 2015), activation of the vStr was significantly increased in SZ patients compared to healthy controls, but our prediction of a hyperactivation of the HPC and the VTA could not be clearly confirmed in this study. Critically, not all SZ patients of our sample were showing acute psychotic symptoms during time of fMRI acquisition, which could possibly explain that we only found a subthreshold hyperactivation not exceeding the statistical significance level. In line with that explanation, we could find a significant correlation of both HPC and VTA activation with the severity of psychotic symptoms. Moreover, the MAM model previously described could rather be a model of psychosis than of SZ, as animals with HPC lesion did show psychotic-like symptoms (Grace, 2010a, b, 2012, 2015, 2016, 2017). In accordance with this, Howes and Kapur (2009) link the dopaminergic dysregulation to psychosis or "psychosis proneness" rather than to SZ. Nevertheless, SZ patients usually do not show constant psychotic symptoms, but also episodes of relative stability or more pronounced negative symptoms. This episodic course of illness cannot be mimicked by the MAM animal model. And so far, there is no other animal model capable for this.

Another rather unexpected result was the finding of an abnormal functional connectivity of the HPC with the VTA/SN and the vStr in SZ patients. On the basis of the MAM animal model we expected to find a positive functional coupling of the HPC with both regions. In contrast, patients showed a negative coupling of both regions opposed to healthy controls, which showed a subthreshold positive coupling of the regions. One possible explanation for the negative coupling could be that the MAM animal model is not optimal to mimic schizophrenia in humans. Another reason could be that different subgroups of patients show different abnormalities and our sample was then to heterogeneous to explore specific deviations. Or it could be that our paradigm is not (only) activating the proposed key regions, but maybe a more

complex mechanism, involving other structures of the brain, which we neglected so far. However, the listed possible reason cannot explain how a positive connectivity might turn into a negative one. It is very unlikely that the switch in direction is based on a direct pathway from one region to the other. The characteristics of a direct pathway as being excitatory or inhibitory can be assumed as genetically determined and stable. In contrast, indirect pathways can be changed very easily, as soon as they contain direct connectivity which is abnormally disrupted, reduced or dysfunctional (see figure 10). For example, when a third region is showing a direct negative coupling with the HPC and a direct positive coupling with the VTA/SN, a reduced direct coupling between HPC and VTA/SN can lead to negative functional connectivity result in PPI analyses. As a consequence, the disruption of one direct pathway can lead to a bunch of indirect pathways being abnormal.

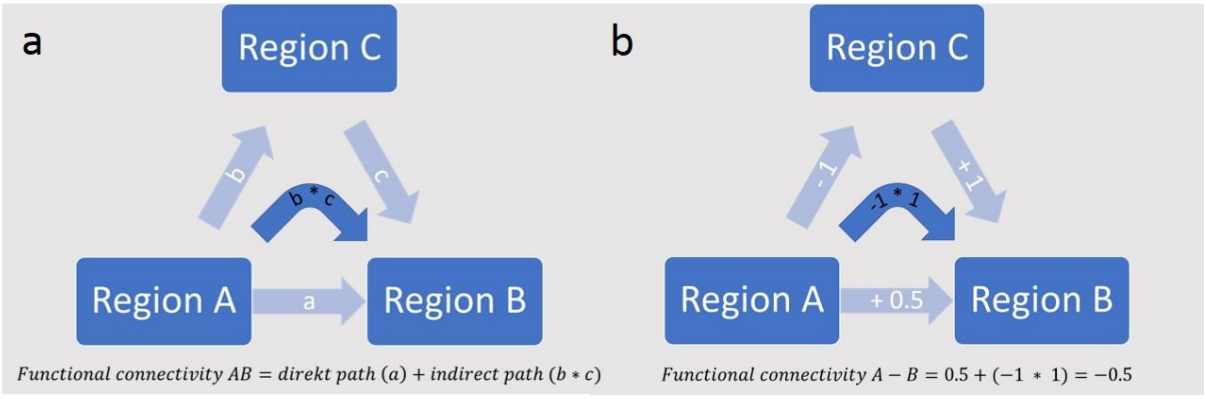


**Figure 10.** Example for reproduction of functional connectivity coefficients with direct and indirect pathways.

With the use of PPI analyses, as described in the two studies, it is neither possible to determine whether an observed connectivity is direct or indirect nor to infer the direction of the connectivity. In this aspect, the interpretability of our data, particularly of the aberrant negative functional connectivity, is very limited. Nevertheless, it can be said that there is a massive disturbance of functional connectivity in the SZ patients, affecting multiple couplings.

Yet, there are no connectivity abnormalities reported for the MAM model of SZ. Therefore, the current findings can be used to guide further research with this specific animal model. Until now, it is not possible to draw any direct conclusions about the validity of the MAM model of SZ.

Interestingly, BD patients showed a very similar pattern of abnormal connectivity of the HPC with VTA/SN and vStr compared to SZ patients, despite partly opposite findings regarding reward-dependent activation of these regions. Again, this underlines that functional connectivity is a very fragile characteristic of the brain, which can be disrupted in multiple

ways. Regardless of this commonality in abnormal functional coupling, it is possible that the cause and the underlying mechanism differ completely in BD patients.

Current animal models of BD do not show the specific hippocampal dysfunction as the MAM model for SZ. Nevertheless, we could find evidence for hyperactivation of the HPC in our study with a minimally to severely depressed BD patient group - although this hyperactivation was observable only at a subthreshold level. However, it is not clear whether a hippocampal dysfunction might play a role for manic or psychotic symptoms in BD. Furthermore, functional connectivity of the HPC was abnormal in this group of euthymic and depressed BD patients. Our findings could also be used to guide further research with animal models of BD, emphasizing the need to study more intensively the impact of a dysfunctional hippocampus on the disorder.

## 4.3 Transdiagnostic commonalities and differences

In this thesis, (1) I am replicating previous studies showing hyperactivation of the vStr in SZ patients and hypoactivation of the vStr in BD patients; (2) I am showing that psychotic symptoms in SZ patients are related to hippocampal activation, with SZ patients showing a subthreshold hyperactivation of the HPC compared to healthy controls; and (3) I am demonstrating that both SZ and BD patients show an abnormal functional connectivity of the HPC with the VTA/SN and the vStr.

There has been a long-lasting debate about the separation of SZ and BD with the suggestion of eliminating the diagnostic border between these disorders (Craddock & Owen, 2005; Crow, 1986). Indeed, the symptoms of the disorders are overlapping, with SZ patients showing mood symptoms and BD patients showing psychotic symptoms (Bellivier et al., 2013; Cosgrove & Suppes, 2013; d'Albis & Houenou, 2015; Keshavan et al., 2011; Pearlson et al., 2015; Peralta et al., 2013; Russo et al., 2014; Whalley et al., 2012). It has been suggested, that the disorders are a continuum rather than clearly separated diagnostic entities (Crow, 1986). Evidence for this hypothesis comes from multiple areas of research, showing genetic overlap (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013) and commonalities in cognitive (Ancin et al., 2013; Hill et al., 2014; Krishnadas et al., 2014; Lewandowski et al., 2014; Schretlen et al., 2013, Smith et al., 2009; Wang et al., 2013), as well as in brain structural (Anderson et al., 2013; Cui et al., 2011; De Peri et al., 2012; Haukvik et al., 2014; Hulshoff Pol et al., 2012; Ivleva et al., 2013; Mathew et al., 2014; Molina et al., 2011; Nanda et al., 2014;

Rimol et al., 2010; Womer et al. 2014) and functional (Anticevic et al., 2014; Argyelan et al., 2014; Baker et al., 2014; Chai et al., 2011; Costafreda et al., 2011; Lui et al., 2014; Mamah et al., 2013; Meda et al., 2012, 2014; Ongür et al. 2010; Sepede et al., 2014) abnormalities. Some findings suggest that patients with BD lie between healthy controls and SZ patients, as they often have the same but less severe abnormalities and dysfunctions as the SZ patients (Argyelan et al., 2014; Costafreda et al., 2011; De Peri et al., 2012; Hill et al., 2013; Ivleva et al., 2013; Krishnadas et al., 2014).

One goal of the study was to compare SZ patients and BD patients regarding their reward-related brain activity and functional connectivity. In table 5 transdiagnostic commonalities and differences found in the current study are summarized.

**Table 5** Transdiagnostic commonalities and differences between schizophrenia and bipolar disorder

| | **Brain activation** | | | **Left HPC functional connectivity** | | **Right HPC functional connectivity** | |
|---|---|---|---|---|---|---|---|
| | vStr | VTA/SN | HPC | VTA/SN | vStr | VTA/SN | vStr |
| Schizophrenia patients | ↑ left | (↑) bilateral | (↑) bilateral | n.s. | n.s. | n.s. | - bilateral |
| Psychotic symptoms | n.s. | + bilateral | + left | - bilateral | n.s. | n.s. | n.s. |
| Bipolar patients | (↓) right | (↑) bilateral | (↑) bilateral | - left | n.s. | n.s. | n.s. |
| Depressive symptoms | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | - right |
| Schizophrenia patients vs. Bipolar patients | n.s. | | | | | | |

*Abbreviations:* HPC, hippocampus; n.s., not significant; SN, substantia nigra; vStr, ventral striatum; VTA, ventral tegmental area. ↑, hyperactivation; ↓, hypoactivation; +, positive correlation; -, negative correlation. Subthreshold effects are reported using brackets.

Although no comparison between SZ and BD patients reached significance, we could find qualitatively opposite vStr abnormalities, in terms of a hyperactivation of the vStr in SZ patients and hypoactivation of the vStr in BD patients. These results replicate findings from Richter et al. (2015) and Trost et al. (2014), respectively.

Common to both disorders is also the implication of dopaminergic abnormalities (Ashok et al., 2017; Howes & Kapur, 2009). In line with this, both patient groups showed a subthreshold hyperactivation of the VTA/SN. Nevertheless, our finding of a hyperactive VTA/SN in depressed BD patients is unexpected, as depressive symptoms and particularly symptoms of anhedonia are thought to be related to hypodopaminergia (Ashok et al., 2017). In contrast, manic and psychotic symptoms are thought to be related to a hyperdominergic state (Ashok et al., 2017; Howes & Kapur, 2009). Supporting this idea, psychotic symptoms in SZ were related to a hyperactive VTA/SN in the SZ study of this thesis.

Psychotic and manic symptoms in BD patients have not been investigated so far in BD patients with the DRD paradigm. The investigation of psychotic symptoms in BD patients constitutes a special challenge for fMRI researchers as psychosis is present mostly in severe cases of depression and mania. In those patients, performance in a task, even a simple task like in the present thesis, can be markedly disrupted. However, to study certain cognitive and emotional processes in patients, it is necessary that the patients are at least capable to perform these cognitive and emotional processes. Not to mention, keeping those patients in the scanner without movement is also a major problem, which must be faced with this kind of patient population.

Another brain region, which was related to psychotic symptoms in the first study of this thesis is the HPC. Hippocampal abnormalities are one of the most replicated findings in SZ patients, although there are studies showing hippocampal abnormalities in BD patients as well (d'Albis & Houenou, 2015). Yet, hippocampal dysfunction is only induced in animal models of SZ but not in animal models of BD. Despite that, we found a subthreshold hyperactivation and abnormal functional connectivity of the HPC not only in SZ but also in BD patients.

All in all, the majority of our findings are in accordance with the view of BD and SZ as overlapping disorders without clear diagnostic borders. In contrast, our results regarding abnormal vStr activations in SZ and BD patients are supporting the assumption that SZ and BD are separate diagnostic entities. Critically, our results indicate that the overlap between both patient groups may at least partly depend on the current symptom state of the patients.

## 4.4 State vs. trait abnormalities

BD and SZ are both lifetime diagnoses. That means that remitted and even long-time symptom free patients still have this diagnosis if they ever fulfilled the criteria for one of the disorders. SZ can have different courses of illness (Barbato, 1998): Some patients do only have one episode of psychosis, whereas other patients have multiple episodes. Moreover, some patients do fully recover, while others exhibit residual symptoms between the episodes. The course of BD can also vary from patient to patient, with patients showing multiple episodes or only a few (Perlis et al., 2006). Furthermore, there are patients having predominant depressive episodes and there are patients suffering from predominant manic episodes (Colom et al., 2006). Furthermore, bipolar I and bipolar II patients have to be distinguished, with the former having at least one full-blown manic episode and the latter having only hypomanic episodes which never fulfill the full diagnostic criteria of a manic episode (APA, 2010, 2013).

There are different approaches in neuroimaging research to study these disorders: One goal is it to find the underlying structural and functional abnormalities of symptoms (state-markers). Another objective is to find neuroimaging markers for higher risk of developing the disorder (trait-markers). One special branch of this kind of research is the endophenotype approach. Endophenotypes are stable traits of patients, which are intermediate between genotype and phenotype (Blangero et al., 2003; Gottesmann & Gould, 2003). Furthermore, there is the aim to detect neuroimaging markers underlying different courses of illness and underlying treatment-response.

Although the design of the studies of this thesis is not optimal to distinguish state vs. trait markers of the disorders, some findings of this thesis are more in favor of a state marker, whereas other findings are more in line with a trait marker:

One way to find trait-markers of disease is to investigate individuals at enhanced genetic risk to develop that specific disorder. In a meta-analysis on structural neuroimaging studies involving individuals at enhanced genetic risk for BD, no significant differences were detected between high-risk individuals and controls in the striatum and hippocampus (Fusar-Poli et al., 2012). State-markers are typically found using correlations with symptom severity. Accordingly, state dependence of striatal activity was shown by Whalley and colleagues (2011).

In the studies of this thesis neither did vStr hyperactivation in SZ patients correlate with psychotic symptom severity nor did vStr hypoactivation in BD patients correlate with depressive symptom severity. Both abnormalities have been established in a mixed sample of

patients with and without current symptoms. These results qualify the reward-related vStr activation as a potential trait marker of both disorders.

In contrast, activation of the HPC and the VTA/SN as well as the functional coupling between both regions have been found to be related to the severity of psychotic symptoms in SZ patients. Therefore, the abnormalities of the HPC and VTA/SN activation might be qualified as possible state markers of psychosis. In line with this, Howes and Kapur (2009) link the dopaminergic dysregulation to psychosis or "psychosis proneness" rather than SZ. Moreover, the MAM model previously described could rather be a model of psychosis than of SZ, as animals with HPC lesion did show psychotic-like symptoms (Grace, 2010a, b, 2012, 2015, 2016, 2017).

The pattern of functional connectivity abnormalities in SZ and BD is not very conclusive. Abnormal functional connectivity of the left HPC and the left VTA/SN was correlated with psychotic symptom severity. Though, in BD patients this abnormal functional connectivity appeared to be state-independent, as there was no significant correlation with depressive symptom severity. Furthermore, psychotic symptoms have not been observed in these patients. Vice versa, abnormal functional connectivity between right HPC and right vStr seemed to be state-independent in SZ patients and state-dependent in BD patients.

Nevertheless, due to the heterogeneity of our samples regarding diverse clinical parameters, like symptom severity, medication, duration of illness, number of episodes, age of onset, etc., these findings are only exploratory and have to be confirmed with an appropriate study design.

## 4.5 Originality and relevance of the findings

Whereas evidence from animal model of SZ for the role of the HPC for the hyperdopaminergic state in SZ is already present (Grace, 2010a, b, 2012, 2015, 2016, 2017), evidence for the role of this mechanism in BD is still missing. Nevertheless, there is substantial overlap between both disorders, regarding multiple factors, such as symptoms, candidate genes, neurotransmitters as well as structural and functional brain abnormalities (Pearlson et al., 2015). One shared feature is the disturbed dopaminergic reward system. For both disorders a dysregulated DA system has been discussed as a possible cause of symptoms (Ashok et al., 2017; Howes & Kapur, 2009). There are multiple findings from both human and animal studies, which demonstrate the relevance of this system for the psychiatric diseases. Nevertheless, not all the findings point to the same direction.

One goal of the present thesis was to investigate, whether functional abnormalities of the HPC and their impact on functional abnormalities of the dopaminergic reward system observed in an animal of SZ are comparable with functional abnormalities of the HPC and the dopaminergic reward system in human patients with SZ. Using a paradigm with context-dependent reward stimuli, we could coactivate the HPC and regions of the dopaminergic reward system (e. g. VTA/SN and vStr).

We could demonstrate that psychotic symptoms of SZ are related to hippocampal and VTA/SN activation. Therefore, this thesis provides evidence from humans that is in line with findings from the MAM animal model of SZ. To our knowledge, this is the first study linking psychosis-related hippocampal functional abnormalities to psychosis-related abnormalities of the dopaminergic reward system. Furthermore, our findings support the current version of the dopamine hypothesis (Howes & Kapur, 2009) that links the dopaminergic dysregulation to psychosis or "psychosis proneness" rather than SZ.

Despite these abnormalities, we could not find a significant impact of these abnormalities on goal-directed behavior, as patients did not differ from healthy controls regarding their distraction from conditioned reward-stimuli. These findings are not conforming with another assumption of dopamine hypothesis of Howes and Kapur (2009), which states that an abnormal DA release and firing of DA neurons lead to an aberrant assignment of salience to innocuous stimuli. I would expect that an increased assignment of salience to reward stimuli, would be associated with higher error rates and slower RTs in response to targets in "desire-reason dilemma" situations. During trials in which targets are paired with neutral stimuli, the target should be the only stimulus that catches attention. Therefore, an immediate response to it can be initiated. In contrast, when a conditioned reward stimulus is present, processing of this stimulus might require attentional resources and therefore a delay in response can be expected. Assuming that both the target and the conditioned reward stimulus are attended, the subject additionally has to trade of the value of the immediate reward against the value of the long-term goal. Assuming that only the conditioned reward stimulus is attended, the subject will probably choose the reward stimulus instead of the target.

Moreover, we could show complex functional connectivity abnormalities within this network of brain regions. These findings have the potential to guide further research on animal model of SZ.

Another aim of this thesis was to explore the same network of brain regions in BD patients to shed further light on transdiagnostic commonalities and differences of BD and SZ patients. We

could show that BD patients show similar functional connectivity abnormalities as SZ patients. Therefore, this thesis is revealing an overlap between both disorders and providing further evidence against a strict diagnostic border between these disorders.

Similar to SZ patients, BD patients showed a subthreshold hyperactivation of VTA/SN and HPC. This alteration might be relevant for psychotic symptoms in BD.

Reward-related vStr activation abnormalities have been found in both SZ and BD patients. Critically, the abnormalities qualitatively differed from each other, with a hyperactivation in SZ patients and a hypoactivation in BD patients. The abnormalities have not been related to psychotic symptoms in SZ patients or to depressive symptoms in BD patients. Thus, the evidence is pointing to vStr activation as a state-independent marker that should be tested for its applicability as an endophenotype marker.

Altogether, this thesis is bringing important new impulses for further translational and transdiagnostic research and is another important piece of the puzzle to understand normal and abnormal brain function. Moreover, the DRD paradigm with context-dependent reward stimuli has been shown to be useful for the further research on SZ and BD.

## 4.6 Limitations

With the first project of my thesis I wanted to translate findings from animal models to humans. However, some general problems are inherent to translational projects. The most important issue is that human research is restricted to non-invasive methods. Accordingly, we could not directly stimulate the HPC to investigate activity changes of the dopaminergic system. Instead, we could only use experimental, in our case visual, stimuli, which are known to activate the respective regions of the brain. Critically, these stimuli and the task related to these stimuli do not only activate our regions of interest, but a widespread network of cortical and subcortical brain regions. Thus, we cannot observe the "pure" interaction of our ROIs. Instead, these interactions are intermixed in multiple ways with input from other regions of the brain. Furthermore, we do not know the direction of information flow in this system. As a result, every abnormal connectivity found in both studies, can include multiple possible anatomical pathways and have multiple possible reasons.

Other limitations of the present studies are inherent to the use of fMRI. FMRI uses the BOLD contrast, which is only a very indirect measure of neuronal activity and is thought to reflect

peri-synaptic activity rather than the spiking rate of individual neurons (Ekstrom, 2010). Due to the fact that the BOLD signal is relatively slow, with duration of multiple seconds, we are not able to track fast neuronal changes. In addition, the spatial resolution of the fMRI signal is very low, revealing only information about large groups of neurons in a brain region. As brain regions normally consist of different types of neurons, with different types of neurotransmitters, we cannot draw any conclusion from this research about processes at this level. Thus, we cannot directly infer whether there are dopaminergic abnormalities or not, although we investigate regions of the dopaminergic reward system. Instead, we can only make indirect inferences, based on the idea that the vStr is mainly receiving dopaminergic input.

Further limitations arise from the heterogeneity of our patient samples regarding diverse clinical parameters, such as symptom severity and constellation, medication, duration of illness, number of episodes, age of onset, etc. All these factors could have an impact on abnormalities of hippocampal activation and functional connectivity. On the one hand, that means that the results could be different with other sample characteristics, and on the other hand, that we cannot draw any conclusions about specific subgroups or states of the illness. Furthermore, this heterogeneity could be the reason why some group comparisons did not reach significance. Nevertheless, variation is required to find correlations. Without the variation in symptom severity the correlations with brain activation and connectivity would probably not have been significant.

## 4.7 Outlook

Although the study was designed to replicate animal findings in humans, the other way of translational research – from the human to the animal – is also part of the process of understanding normal and abnormal brain function. The finding of an abnormal functional connectivity between HPC and VTA/SN is an aspect that was not considered so far in the MAM model of SZ. Nevertheless, future studies should address this aspect. Furthermore, as also BD patients were showing these abnormalities, it should be considered in animal models of BD as well.

Some of the findings described before were state-dependent. Particularly, HPC activation, VTA/SN activation and HPC-VTA/SN coupling have been shown to be dependent on the severity of psychotic symptoms. Therefore, as a next step, patients with and without psychotic symptoms, should be separately compared to healthy controls.

Furthermore, to better understand state dependent and independent processes in BD, manic, depressive and euthymic patients should be investigated more separately in future studies. Ideally, the same subjects should be scanned during different time points, spanning different states of illness. To further elucidate the diagnostic boundaries of SZ and BD, it could be helpful to examine severe cases of BD with psychotic symptoms to evaluate their similarities and differences with SZ.

As we cannot exclude, that some of the findings are related to medication effects, future studies should try on the one hand to shed light on neurofunctional changes related to medication and on the other hand investigate medication-naïve patients at their first episode of illness. Especially for BD patients, this can be quite problematic, as many of them are misdiagnosed as unipolar when they first get a depressed episode.

The transdiagnostic finding of an abnormal HPC-VTA/SN functional connectivity should also be considered as a possible endophenotype marker in the future. Although more research with unaffected relatives of SZ and BD patients is necessary to approve this. Furthermore, future studies should try to shed further light on the finding of the negative HPC-VTA/SN and HPC-vStr coupling, which was not present in healthy controls. For example, a better spatial resolution could be helpful, to better differentiate subregions within the HPC and the VTA.

Another important research area, which could use the findings of the present thesis, is the search for neuroimaging markers predicting treatment response. Although antidopaminergic drugs are used both for treatment of SZ and BD, it is still not known why some patients do not respond to the treatment targeting the dopamingergic system.

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# III. Supplement

**Table S 1** Whole-brain reward-related brain activations in the "desire context" in schizophrenia patients and healthy controls

| **Region** | **Schizophrenic patients** | **Healthy controls** | **Schizophrenic patients > Healthy controls** | **Healthy controls > Schizophrenic patients** |
|---|---|---|---|---|
| | MNI coordinates (*t*-values) | MNI coordinates (*t*-values) | MNI coordinates (*t*-values) | MNI coordinates (*t*-values) |
| R Cerebellum | 9 -43 -5 (4.99) | 33 -52 -29 (6.15) | n.s. | n.s |
| | 33 -31 -29 (5.02) | 3 -64 -32 (5.31) | | |
| L Cerebellum | -6 -40 4 (5.12) | -27 -55 -20 (5.07) | n.s. | n.s. |
| | | -9 -76 -29 (5.05) | | |
| R IPL | 42 -58 46 (5.44) | 48 -55 46 (5.67) | n.s. | n.s. |
| | 48 -40 46 (5.14) | 48 -40 49 (4.80) | | |
| L IPL | -39 -55 46 (5.77) | -45 -58 49 (5.24) | n.s. | n.s. |
| R MFG | n.s. | 36 50 7 (4.91) | n.s. | n.s. |
| | | 48 26 40 (4.83) | | |
| | | 27 17 49 (4.74) | | |
| L MFG | n.s. | -39 50 4 (5.75) | n.s. | n.s. |
| R SFG | n.s. | 27 26 55 (4.96) | n.s. | n.s. |
| R Superior orbital | n.s. | 21 56 -2 (5.14) | n.s. | n.s. |
| R Insula | n.s. | 33 20 -8 (6.10) | n.s. | n.s. |
| L Insula | n.s. | -30 23 -5 (5.28) | n.s. | n.s. |
| L/R posterior-medial frontal | n.s. | -6 -4 55 (5.27) | n.s. | n.s. |
| L/R ACC | n.s. | -12 35 22 (4.83) | n.s. | n.s. |
| L/R MCC | n.s. | -3 -31 37 (5.15) | n.s. | n.s. |
| L/R PCC | -6 40 22 (4.70 | n.s. | n.s. | n.s. |
| R Precuneus | n.s. | 12 -64 43 (4.76) | n.s. | n.s. |

| | | | | |
|---|---|---|---|---|
| | | 6 -70 43 (4.80) | | |
| L Precuneus | -3 -46 46 (5.16) | 0 -73 40 (4.71) | n.s. | n.s. |
| R ITG | n.s. | 60 -43 -11 (4.69) | n.s. | n.s. |
| L ITG | n.s. | -57 -49 -14 (5.44) | n.s. | n.s. |
| R MTG | n.s. | 63 -31 -11 (4.91) | n.s. | n.s. |
| R MOG | 33 -70 28 (5.04) | 33 -79 25 (4.72) | n.s. | n.s. |
| R Precentral | 33 -19 43 (4.99) | n.s. | n.s. | n.s. |
| L Precentral | n.s. | -33 -19 64 (4.81) | n.s. | n.s. |
| R Thalamus | n.s. | 9 -7 -2 (4.74) | n.s. | n.s. |
| L Str | -18 8 -11 (4.71) | n.s. | n.s. | n.s. |
| | -18 8 -2 (4.78) | | | |
| R HPC | 21 -31 -17 (5.11) | n.s. | n.s. | n.s. |

*Abbreviations:* ACC, Anterior Cingulate Cortex; HPC, Hippocampus; IPL, Inferior Parietal Lobe; ITG, Inferior Temporal Gyrus; L, left; MCC, Midcingulate Cortex; MFG, Middle Frontal Gyrus; MNI, Montreal Neurological Institute; MOG, Middle Occipital Gyrus; MTG, Middle Temporal Gyrus; n.s., not significant; PCC, Posterior Cingulate Cortex; R, right; SFG, Superior Frontal Gyrus; Str, Striatum. Effects on regional brain activation were significant at a level of $p < .05$, FWE-corrected for the entire brain.

**Table S 2** Whole-brain reward-related brain activations in the "desire context" in bipolar patients and healthy controls

| **Region** | **Bipolar patients**<br><br>MNI coordinates<br>(*t*-values) | **Healthy controls**<br><br>MNI coordinates<br>(*t*-values) | **Bipolar patients**<br>**>**<br>**Healthy controls**<br>MNI coordinates<br>(*t*-values) | **Healthy controls >**<br>**Bipolar patients**<br>MNI coordinates<br>(*t*-values) |
|---|---|---|---|---|
| R Cerebellum | n.s. | 21 -58 -20 (6.45)<br>3 -67 -32 (4.99)<br>3 -70 -23 (4.76) | n.s. | n.s. |
| L Cerebellum | -12 -34 -26 (4.68) | -30 -52 -23 (5.20)<br>-9 -76 -29 (4.88) | n.s. | n.s. |
| R IPL | 39 -58 46 (5.00) | 39 -67 46 (5.38)<br>48 -40 49 (5.09) | n.s. | n.s. |
| L IPL | -36 -61 49 (5.43) | -42 -58 52 (5.26) | n.s. | n.s. |
| L IFG (pars Orbitalis) | n.s. | -39 44 -14 (4.70) | n.s. | n.s. |
| R MFG | n.s. | 45 23 46 (5.23) | n.s. | n.s. |
| L MFG | n.s. | -39 50 4 (5.94) | n.s. | n.s. |
| R SFG | n.s. | 27 26 55 (5.02) | n.s. | n.s. |
| R Superior orbital | n.s. | 24 59 1 (4.97) | n.s. | n.s. |
| R Insula | n.s. | 36 20 -8 (6.43) | n.s. | n.s. |
| L Insula | n.s. | -30 20 -5 (5.28) | n.s. | n.s. |
| L/R posterior-medial frontal | n.s. | -6 -4 55 (4.88) | n.s. | n.s. |
| L/R ACC | n.s. | -12 35 22 (4.97)<br>-3 5 31 (5.09) | n.s. | n.s. |
| L/R MCC | | -6 32 40 (4.86) | n.s. | n.s. |
| R Precuneus | 6 -67 43 (5.74) | n.s. | n.s. | n.s. |

| | | | | |
|---|---|---|---|---|
| R ITG | 51 -58 -17 (4.77) | n.s. | n.s. | n.s. |
| | 57 -49 -17 (4.75) | | | |
| L ITG | n.s. | -57 -46 -14 (5.11) | n.s. | n.s. |
| R MTG | 60 -37 -14 (5.04) | 63 -31 -11 (4.98) | n.s. | n.s. |
| L Precentral | n.s. | -33 -16 67 (4.78) | n.s. | n.s. |
| | | -30 -19 64 (4.69) | | |
| L Calcarine Gyrus | n.s. | -18 -58 4 (4.72) | n.s. | n.s. |
| L Fusiform Gyrus | -18 -34 -17 (4.76) | n.s. | n.s. | n.s. |
| R Thalamus | n.s. | 9 -7 -2 (5.04) | n.s. | n.s. |
| L Str | n.s. | -9 11 -5 (4.84) | n.s. | n.s. |
| R Str | n.s. | 12 8 -2 (5.09) | n.s. | n.s. |
| R HPC | n.s. | 18 -28 -8 (4.67) | n.s. | n.s. |

*Abbreviations:* ACC, Anterior Cingulate Cortex; HPC, hippocampus; IFG, inferior frontal gyrus; IPL, Inferior Parietal Lobe; ITG, Inferior Temporal Gyrus; L, left; MCC, Midcingulate Cortex; MFG, Middle Frontal Gyrus; MNI, Montreal Neurological Institute; MOG, Middle Occipital Gyrus; MTG, Middle Temporal Gyrus; n.s., not significant; R, right; SFG, Superior Frontal Gyrus; Str, Striatum. Effects on regional brain activation were significant at a level of $p < .05$, FWE-corrected for the entire brain.

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