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Transdiagnostic signatures of functional brain responses during reward processing in the extended moods-psychosis spectrum

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ABBREVIATIONS

ACC: anterior cingulate cortex

ANCOVA: Analyses of Covariance

ASD: autism spectrum disorder

BAS: behavioral activation system

BDI: Beck Depression Inventory

BOLD: blood-oxygenation-level-dependent

BP: bipolar disorder

CGI: Clinical Global Impression Scale

CPZ-e: chlorpromazine dose equivalents

DSM: Diagnostic and Statistical Manual of Mental Disorders

ED50: mean effective daily dose

EPI: echo-planar imaging

Fb: feedback

FD: frame-wise displacement

FIRMM: frame-wise integrated real-time MRI monitoring

fMRI: functional magnetic resonance imaging

FOV: field of view

FPN: fronto-parietal network

FWE: family-wise error

GABA: gamma-aminobutyric acid

GLM: general linear model

HAM-D: Hamilton Depression Scale

HC: healthy control

HiTOP: Hierarchical Taxonomy of Psychopathology

HRF: hemodynamic response function

ICCs: intra-class correlation coefficients

ICD: International Classification of Diseases

IPL: inferior parietal lobule

IQR: interquartile range

LD: linkage disequilibrium

MD: major depressive disorder

ME: main effect

mFD: mean frame-wise displacement

MID: monetary incentive delay task

MNI: Montreal Neurological Institute MRI: magnetic resonance imaging

PANSS: Positive and Negative Symptom Scale

PCA: principal component analysis

PGR: polygenic risk

PROMO: prospective motion correction

QC: quality control

RDoC: Research Domain Criteria

ROI: region of interest

SCID-I: Structured Clinical Interview for DSM-IV-TR axis I disorders

SE: standard error

SVC: small volume correction

SPQ: Schizotypal Personality Questionnaire

SSRI: selective serotonin uptake inhibitor

SZ: schizophrenia

TE: echo time

TR: repetition time

VLMT: verbal learning memory test

vST: ventral striatum

VTA: ventral tegmental area

YMRS: Young Mania Rating Scale

1 INTRODUCTION

1.1 Dimensional Psychiatry – a new approach in psychiatry

1.1.1 Categorical vs. dimensional approaches to psychopathology

Since the middle of the last century, attempts to classify mental disorders based on standard criteria and a common language guide the diagnostic procedure and treatment of psychiatric conditions. The most influential diagnostic systems for mental health (the *International Classification of Diseases* (ICD; World Health Organization, 1993) and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM; American Psychiatric Association, 2013) greatly reduced international variations on prevalence estimates, initiated research and improved the acceptance and clinical care of patients with mental disorders. By considering the number and duration of symptoms, disorder courses or treatment responses and the presence of distress or impairment, these traditional diagnostic systems enable reliable diagnosis. Meanwhile, our clinical care system highly depends on reliable diagnostics, as they determine which patients are ill enough to justify treatment (Goldberg, 2000). The symptom-based nature of the diagnostic systems greatly improved the reliability of clinical diagnosis while the etiology of the postulated disorder entities is beyond the scope of these classification systems (Walter, 2017). Within the last decade, the validity of the simplification that accompanies the descriptive grouping of patients in distinct disorder categories was increasingly questioned. Specifically, as psychopathology was shown to exist on a continuum with normal range-functioning, the division of people in binary “health” or “disease” states neglects the clinical significance of symptoms below or in between categorical thresholds (Helzer, Kraemer, & Krueger, 2006; Kotov et al., 2017). In addition, neuroscientific evidence suggests a substantial overlap between clinical phenotypes and genetics across separate disorder categories (Gandal et al., 2018). Therefore, a more fine-grained transdiagnostic and dimensional characterization can supplement (or even supplant) categorical diagnosis and inform our understanding of the development and the underlying biological mechanisms of severe mental disorders. While these considerations already began to influence the new versions of the DSM-5 (American Psychiatric Association, 2013) and the ICD-11 (World Health Organization, 2020), which for example aggregate overlapping disorders into spectrum disorders (e.g., autism-spectrum-disorders) or add severity ratings to diagnoses, the categorical nature of the diagnostic systems is still largely preserved (Brown & Barlow, 2005). Meanwhile, modern approaches, like

the Research Domain Criteria (RDoC) approach of the National Institute of Mental Health or the Hierarchical Taxonomy Of Psychopathology (HiTOP, Kotov et al., 2017) developed novel concepts on how to restructure psychiatric nosology towards a more dimensional conceptualization. Hereby, the RDoC initiative is in quest for core neurobiological mechanisms that characterize common features across psychiatric conditions (Cuthbert, 2014; Insel et al., 2010). In order to explore core brain-behavior domains assembling basic dimensions of functioning, six major domains (e.g., the Positive and Negative Valence System or the Cognitive System) are studied along the full range of human behavior from normal to abnormal on multiple investigation levels (e.g., genomics, circuits, behavior) and across the lifespan (NIMH, n.d.). While this approach adds substantial value for research questions by addressing psychiatric nosology on a very basic level, the translation and applicability of findings to clinical practice and health system organization is difficult. The HiTOP approach is much closer to the clinical work as it is based on existing clinical constructs, but with a clear dimensional, quantitative and evidence-based focus on psychiatric phenotypes. Specifically, HiTOP classifies symptom constellation on different levels of generality: The basis constitutes individual signs and symptoms that are combined into homogeneous components or traits that assemble empirically-derived syndromes within psychopathology spectra, all contributing to a general psychopathology g-factor (Renaissance School of Medicine at Stony Brook University, n.d.). This approach reduces within-disorder heterogeneity, predicts comorbidity and has a strong dimensional view. However, similar to traditional diagnostic systems, the HiTOP taxonomy is descriptive in nature and does not directly target the etiology, pathophysiology and treatment response of mental disorders (Wittchen & Beesdo-Baum, 2018).

Overall, refining traditional diagnostic categorization procedures based on accumulating knowledge about underlying biological processes (e.g., with the help of the RDoC initiative) and quantitative, evidence-based descriptions of dimensional psychiatric phenotypes (e.g., with approaches like HiTOP) will help to minimize the shortcomings of traditional taxonomies. However, the value of consistency, transparency, efficiency and applicability of psychiatric nosology should not be underestimated. This thesis is concerned with the unification of different approaches on psychiatric nosology to optimally exploit individual strengths and advantages. In a first step, brain functioning alterations in the Positive Valence System between disorder categories in the extended moods-psychosis spectrum are studied (Figure 1.1a). Secondly, to unravel transdiagnostic mechanisms underlying reward network alterations, dimensional brain-behavior associations are investigated (Figure 1.1b). Lastly, I will focus on the biological mechanism

underlying reward network alterations and propose a novel mechanism with a prominent specificity for psychotic disorders while incorporating different units of analyses (Figure 1.1c). Notably, this thesis demonstrates the potential of neuroimaging biomarkers in explaining brain-behavior relationships for broad and overarching symptom domains (i.e., spectra in the HiTOP language) that cut across traditional disorder categories (Cuthbert, 2014; Insel et al., 2010). This approach may add to current knowledge about the underlying mechanisms of mental disorders, from which valuable ideas for treatment development may arise.

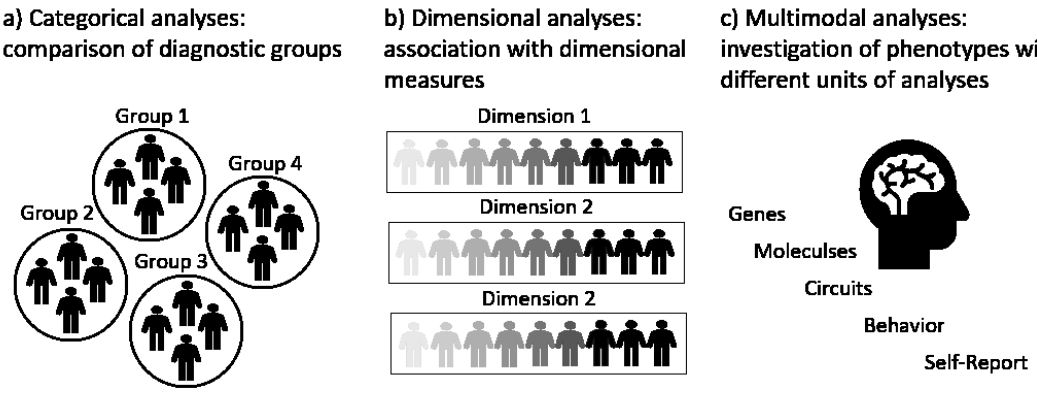

Figure 1.1: Analyses strategies.

1.1.2 The Reward System – a prime candidate for transdiagnostic and dimensional analyses

Alterations in reward sensitivity or reinforcement-dependent learning play a key role in psychiatric disorders. Reward processing shapes goal-directed behavior and adaptive decision-making through an iterative learning process in order to minimize harm and enhance well-being (Oldham et al., 2018). Specifically, reward facilitates learning through positive or negative reinforcement, which influences the probability of shown behaviors in the future. While many different conceptualizations of reward-related sub-processes exist (Keren et al., 2018; Kring & Barch, 2014), two basic, temporally and neurologically distinct mechanisms relate to the anticipation and consumption of reward (Berridge & Robinson, 2003, 2016). Reward anticipation reflects the ability to represent a potential future incentive and has been implicated in numerous neurodevelopmental and psychiatric conditions (Dichter, Damiano, & Allen, 2012), including psychotic (Chase, Loriemi, Wensing, Eickhoff, & Nickl-Jockschat, 2018; Leroy et al., 2020; Radua et al., 2015) and affective (Keren et al., 2018; Kujawa & Burkhouse, 2017) disorders. Dysfunctional reward-processing is assumed to contribute to the development (Hanson et al., 2017; Keren et al., 2018) as well as the course of psychiatric symptoms (Corral-Frías et al., 2015; Dennison et al., 2016; Goldstein et al., 2020; Kujawa et al., 2016; Kujawa, Hajcak, et al., 2019; Sandre et al., 2019)

and to predict mental and physical health complications (Danner, Snowdon, & Friesen, 2001; Keren et al., 2018; Kujawa, Burkhouse, et al., 2019; Salovey, Rothman, Detweiler, & Steward, 2000; Tugade, Fredrickson, & Barrett, 2004). The importance of reward processing mechanisms for understanding mental health problems is accounted for within the RDoC approach, where reward-related mechanisms represent one of the six basic functioning domains, the Positive Valence System. This domain comprises distinct behavioral and physiological processes involved in anticipating, obtaining, and responding to positive internal or external stimuli (NIMH, n.d.; Olino, 2016).

Within the following sections I will briefly summarize the level of knowledge about the neural signatures of reward processing specifically focusing on reward anticipation before reviewing studies investigating neural reward processing alterations between and across psychiatric disorders.

1.2 Neural correlates of human reward processing

1.2.1 The reward network

The reward circuit is a complex neural network most consistently related to the fronto-striatal circuit (Nusslock & Alloy, 2017). As outlined above, reward processing can be distinguished into reward anticipation and reward consumption, which are associated with distinct neural circuits (Dillon et al., 2008; Rademacher et al., 2010). While reward consumption has been linked to opioid and cannabinoid release predominantly in the medial prefrontal cortex and subcortical regions, reward anticipation has been associated with dopaminergic functioning (Kringelbach & Berridge, 2010; Salimpoor et al., 2011; Yan et al., 2016). Specifically, dopaminergic midbrain neurons mainly within the ventral tegmental area (VTA) project to subcortical regions processing the rewarding properties of stimuli. The ventral striatum (vST), encompassing the nucleus accumbens and ventromedial parts of the caudate and putamen, has been implicated as a key hub for reward anticipation (Haber, 2011). Animal and human research consistently linked activation within the vST to the exposure of both primary (e.g., pleasant taste, sound and sight) and secondary (e.g., monetary) reward-indicating cues (Wilson et al., 2018). Substantial evidence indicated that reward-related brain responses in the vST are modulated by dopaminergic functioning (e.g., Schott et al., 2008) and related to reinforcement learning through prediction errors, a striatal

dopamine-encoded signal that indicates the difference between anticipated and experienced reward (Schultz, 1997, 2016).

The vST itself is densely interconnected and receives input from various cortical areas, especially sub regions of the prefrontal cortex. For example, key nodes of the salience network, including the anterior cingulate cortex (ACC), the anterior insula as well as parts of the central executive and default mode network have been observed during reward anticipation (Gradin et al., 2013; Wilson et al., 2018; see Figure 1.2) and linked to the evaluation and magnitude of value and probability estimation of reward (Liu, Hairston, Schrier, & Fan, 2011). In addition, the amygdala and hippocampus have been implicated in the emotional and contextual coding of environmental stimuli (Haber, 2011). These various inputs are integrated within the vST, highlighting the pivotal role of striatal brain regions for investigating transdiagnostic reward network alterations (Nusslock & Alloy, 2017).

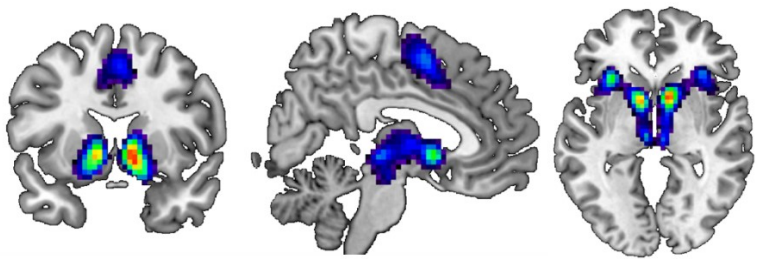

Figure 1.2: Neural signatures of reward anticipation, centrally involving the ventral striatum (own unpublished illustration).

1.2.2 Neural reward processing in *categorical* psychiatric disorders

Schizophrenia (SZ)

Impairments in motivation and salience processing have long been considered cardinal symptoms in SZ and are already present in the earliest stages of the disorder (Foussias & Remington, 2010; Schlosser et al., 2014). These abnormalities have been consistently linked to reward processing abnormalities, specifically blunted striatal functioning during reward anticipation (Chase et al., 2018; Leroy et al., 2020; Radua et al., 2015). Thereby, fronto-striatal circuit dysfunctions have been related to alterations in the dopamine system, a primary pathology in SZ (Fusar-Poli & Meyer-Lindenberg, 2013; Howes & Kapur, 2009; Howes et al., 2017). However, the mechanisms linking dopaminergic abnormalities in SZ to reward processing alterations are still a subject of intense debate (Leroy et al., 2020). The most prominent theory is the aberrant salience hypothesis, which suggests that the inappropriate assignment of attention (or salience) to irrelevant stimuli, a pivotal

observation during psychotic episodes, is a result of chaotic dopaminergic firing in mesolimbic reward circuits (Kapur, 2003; see section 1.3.2 for a detailled description). In line with this assumption, substantial evidence indicates that vST alterations are dimensionally related to the severity of positive psychotic symptoms (Juckel et al., 2006; Nielsen et al., 2012). However, also negative symptoms, specifically anhedonia and avolition, have been linked to dopamine dysfunction (Juckel et al., 2006; Pogarell et al., 2012) and reduced reward-related brain responses in the vST (Dowd & Barch, 2012; Gradin et al., 2013; Yan et al., 2016). Hägele and colleagues (2015) pointed out that the association between negative or depressive symptoms and vST reactivity might reflect a diminished attribution of motivational salience to reward-indicating cues reflected by dopaminergic alterations.

Overall, blunted reward network functioning during reward anticipation is a well-established phenotype in SZ. However, while cardinal symptoms of SZ might cause or at least influence these alterations, the mechanisms underlying altered vST reactivity are still insufficiently understood. Supplementing the comparison of neural responses between patients and non-affected subjects with dimensional and transdiagnostic approaches might help to unravel the neurobiological underpinnings of reward network dysfunction in SZ.

Major Depression (MD)

MD is characterized by depressed mood and anhedonia (American Psychiatric Association, 2013), a diminished interest and ability to derive pleasure from pleasant sensory stimuli or activities (Fawcett, Clark, Scheftner, & Hedeker, 1983; Snaith, 1993). Both symptom domains are associated with aberrant reward processing, especially reward anticipation (Höflich, Michenthaler, Kasper, & Lanzenberger, 2018; Pizzagalli et al., 2008) and altered dopamine neurotransmission (Belujon & Grace, 2017; Brown & Gershon, 1993; Tremblay et al., 2005) suggesting overlapping neurobiological mechanisms. In line with this hypothesis, the vast majority of studies reported reduced reward system responses in MD (Pizzagalli et al., 2009; Robinson, Cools, Carlisi, Sahakian, & Drevets, 2012; Satterthwaite et al., 2015; Smoski et al., 2009; Stoy et al., 2012). However, experimental findings on reward network alterations in MD vary considerably and even meta-analytical approaches yielded different and inconsistent findings (Keren et al., 2018; Müller et al., 2017; Zhang et al., 2013). For example, a recent meta-analysis found reduced vST activation in MD during reward feedback, while vST-activation differences during reward anticipation were weaker and primarily observed in younger subjects under 18 years (Keren et al., 2018). Blunted vST reactivity to reward-related cues has been observed in adolescents with subthreshold MD and

found to predict the onset of MD in adolescents (Stringaris et al., 2015). Besides these developmental effects, differences in medication, task design or the range of depression severity of included patient samples might have contributed to the inconsistencies found in previous studies (Müller et al., 2017; Satterthwaite et al., 2015). The use of dimensional measures of anhedonia might help to quantify the contribution of alterations in reward anticipation in MD (Keren et al., 2018).

Bipolar Disorder (BP)

There is substantial evidence that BP overlaps with both, SZ and MD in symptomatology, genetic and environmental risk factors as well as psychopathological mechanism (Carroll & Owen, 2009; Maier, Zobel, & Wagner, 2006; Pearlson, 2015; Schulze et al., 2014). Given that blunted vST reactivity in response to reward-indicating cues is a well-established phenotype across affective and psychotic disorders, it is likely to find similar alterations in BP. In line with the behavioral activation system (BAS) dysregulation model (Alloy & Abramson, 2010; Urosević, Abramson, Harmon-Jones, & Alloy, 2008), a large body of studies using self-report measures and behavioral tasks (Alloy, Olino, Freed, & Nusslock, 2016), suggest elevated reward sensitivity in BP. Moreover, vST activation to reward-indicating cues has been associated to traits related to BP like reward sensitivity (Hahn et al., 2011; Schreuders et al., 2018) and positive urgency states (Johnson, Mehta, Ketter, Gotlib, & Knutson, 2019), a tendency to impulsively engage in regrettable behaviors during positive emotional states (Giovanelli, Hoerger, Johnson, & Gruber, 2013; Johnson, Carver, Mulé, & Joormann, 2013). However, studies on the neurobiological underpinnings of reward network alterations in BP patients are still rare and provide largely inconsistent results (for an overview see Johnson et al., 2019). The variability in mood states but also methodological challenges likely contribute to these inconsistent results. Mood switches in BP are thought to reflect state-dependent dimensional changes in the BAS, specifically hyperactivity during manic and hypoactivity during depressive episodes, respectively. On the other hand, elevated BAS levels are conceptualized as a trait vulnerability marker for BP because BAS scores were shown to predict the severity of manic symptoms (Alloy & Abramson, 2010) as well as the transition to BP in healthy subjects at risk for BP (Alloy et al., 2012; Kollmann, Scholz, Linke, Kirsch, & Wessa, 2017). Moreover, higher BAS scores were found to remain elevated after the remission from manic symptoms (Meyer, Johnson, & Winters, 2001). The dissociation between state-effects and trait-markers remains a major challenge when studying BP which may contribute to the limited number of studies and small sample sizes (mostly less than 20; see Johnson et al., 2019 for an overview).

Furthermore, the use of different task designs is likely to influence the direction of alterations: While incentive delay tasks tentatively found reduced vST activation, card-guessing paradigms rather reported elevated vST activation during reward anticipation (Johnson et al., 2019).

The inconsistencies of results and challenges in studying BP highlight the need for transdiagnostic and dimensional investigations that focus on functional domains rather than distinct disorder entities.

Autism spectrum disorder (ASD)

Reward processing alterations have also been reported for neurodevelopmental disorders such as ASD (Dichter, Damiano, et al., 2012). Although the clinical characteristics of ASD are considerably different from psychiatric disorders (e.g., SZ, BP and MD), similar neurodevelopmental pathways with shared genetic alterations (e.g., Carroll & Owen, 2009; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Sullivan et al., 2012; Jim van Os & Kapur, 2009), high comorbidity rates (Stahlberg, Soderstrom, Rastam, & Gillberg, 2004) and commonalities in social processing impairments (Chung, Barch, & Strube, 2014; King & Lord, 2011) suggest the existence of shared psychopathological mechanisms. Reward processing is a key target for such transdiagnostic investigations, given the number of studies indicating reward network alterations in ASD (Dichter, Felder, et al., 2012; Dichter, Richey, Rittenberg, Sabatino, & Bodfish, 2012; Park et al., 2016; Scott-Van Zeeland, Dapretto, Ghahremani, Poldrack, & Bookheimer, 2010). It is just recently that Pavăl (2017) linked alterations in the mesocortical reward network to dopamine imbalances in ASD. Specifically, the introduced dopamine hypothesis of autism suggests that the failure to register social experiences as rewarding leads to a reduced motivation to seek social interactions and develop social skills (Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012), and is therefore based on alterations in the dopaminergic reward network (Pavăl, 2017). In fact, the repeatedly reported dopamine dysfunctions in ASD (Canitano, 2006; Cohen et al., 2013; Toda et al., 2006) have been related to alterations in the reward network (Kohls, Chevallier, Troiani, & Schultz, 2012). In addition, impaired mesolimbic dopaminergic signaling was shown to alter specific reward-related behavior in autistic subjects, such as effort-based decision making for rewards (Damiano, Aloi, Treadway, Bodfish, & Dichter, 2012), and dopamine antagonists were shown to improve stereotyped (McCracken et al., 2002; McDougle et al., 2005) and social behavior (Ghaeli, Nikvarz, Alaghband Rad, Alimadadi, & Tehrani Doost, 2014; Scahill et al., 2013). However, the overall number of studies is small and methodological challenges (e.g., heterogeneity of the

disorder, small samples) call for additional studies in order to investigate the role of reward functioning alterations in ASD and its relation to other mental disorders.

1.2.3 Neural reward processing *across* psychiatric conditions

Despite the converging literature on blunted reward network functioning throughout psychiatric conditions, the comparison of mechanistic theories underlying reward dysfunction highlights the need for transdiagnostic research. Interestingly, very different biological explanations are applied to the exact same finding of altered vST reactivity depending on the investigated diagnostic group, for example aberrant salience processing in SZ (Gradin et al., 2013), anhedonia in MD (Zhang et al., 2013), social motivation deficits in ASD (Chevallier et al., 2012) or behavioral activation dysfunctions and impulsivity in BP (Johnson et al., 2019; Urosević et al., 2008). Hence, the question whether shared or distinct psychological processes lead to the observed alterations cannot be solved through a simple comparison of diagnostic entities. The incorporation of dimensional, transdiagnostic approaches will help to investigate whether differences in reward network functioning are based on disorder-specific pathological mechanisms or relate to the same psychological (dys)function across mental disorders. Previous studies already demonstrated that striatal brain responses are related to dimensional concepts like aberrant salience, anhedonia, depressive symptoms or reward sensitivity throughout psychiatric conditions (e.g., Arrondo et al., 2015; Hägele et al., 2015; Sharma et al., 2017). Most of the existing transdiagnostic studies focused on anhedonia, presumably the earliest candidate for transdiagnostic studies (Harrow, Grinker, Holzman, & Kayton, 1977). More recent work suggests substantial overlap in the biological underpinnings of anhedonia between MD and SZ (Zhang et al., 2016, Sharma et al., 2017), such as blunted vST functioning (Segarra et al., 2016) which involves dysfunctional dopamine neurotransmission in reward circuitry (Ferenczi et al., 2016; Gold et al., 2018). For example, Hägele and colleagues (2015) reported an association of brain responses in the vST during reward anticipation and depressive symptoms across patients with MD, SZ, BP, alcohol dependence and attention-deficit/hyperactivity disorder. However, using single, disorder-specific clinical measures has the disadvantage of showing low variance in healthy subjects and focusing on single psychopathological processes while neglecting other psychological variables. This focus on disorder-specific mechanistic theories and the overall limited number of transdiagnostic studies calls for new approaches to assess dimensional brain-behavior relationships.

1.3 Neuronal salience processing in psychiatric disorders

1.3.1 Genetic underpinnings: Reward-related striatal brain response as an intermediate phenotype for psychosis

The reviewed studies on categorical and dimensional reward dysfunctions across the psychiatric spectrum are based on descriptive group comparisons and correlations with symptom measures. However, these studies do not allow conclusions on the etiology and underlying biological mechanisms of reward processing alterations, which is one of the major criticisms of the current diagnostic systems. The RDoC initiative suggests to incorporate multiple units of analyses, highlighting for example the importance of genetic factors for the etiology of psychiatric disorders. In general, psychiatric disorders are thought to result from complex interactions between multiple genetic and environmental factors (Purcell et al., 2009), whereby the overall genetic risk architecture across distinct mental disorders highly overlap (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Exploring the genetic background of transdiagnostic imaging phenotypes (i.e., blunted reward anticipation) might help to unravel open questions such as the disorders-specificity, etiology and biological mechanisms of reward processing alterations. One promising approach is the investigation of unaffected first-degree relatives of patients with psychiatric disorders. These familial high-risk populations share an enriched set of risk genes without manifest clinical symptoms, which rules out confounding factors like medication, illness-duration or current symptom severity (Cao, Dixson, Meyer-Lindenberg, & Tost, 2016; Rasetti & Weinberger, 2011). Neuroimaging measures that can be linked to both genetic susceptibility and psychiatric symptomatology are referred to as intermediate phenotypes. These biological phenotypes are more directly influenced by the genetic predisposition. In addition, compared to illness-related behavioral abnormalities, intermediate phenotypes are closer to the molecular effects of risk genes (Cao, Dixson, et al., 2016; Meyer-Lindenberg, 2010; Rasetti & Weinberger, 2011).

Previous neuroimaging studies revealed that blunted vST activation during reward anticipation qualifies as an intermediate phenotype (Grimm et al., 2014) as it is quantitative and partly heritably (Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009), can reliably be measured with state-of-the-art incentive delay tasks (Grimm et al., 2014), is altered in psychiatric patients as well as in populations with high familial risk for schizophrenia (de Leeuw, Kahn, & Vink, 2015; Grimm et al., 2014; Wotruba et al., 2014) and linked to polygenic risk scores for psychosis (including SZ

and BP patients; Lancaster et al., 2016). While blunted reward-related vST-reactivity is a well-established observation in affective disorders, no study to date observed similar alterations in unaffected relatives with MD and BP (Kollmann et al., 2017; Singh et al., 2014). While these results suggest stronger genetic underpinnings of blunted reward network functioning in SZ, a final conclusion is hampered by the small number of studies investigating first-degree relatives with affective disorders as well as methodological problems (e.g., small sample size) and heterogeneities between studies (e.g., investigating children/adolescents vs. adults). The joint investigation of first-degree relatives of patients across the moods-psychosis spectrum would greatly inform the discussion of disorder-specific genetic underpinnings of altered reward processing.

1.3.2 Mechanistic insights: Dopamine as a mediator of salience

While reward-related brain activation especially in the vST seems to be a transdiagnostic phenotype with a genetic underpinning most prominently for psychosis, the biological mechanisms underlying these alterations are still not fully understood. Substantial evidence suggests that dopaminergic system dysfunction underlies reward processing differences in mental health disorders (Dubol et al., 2018). Specifically, previous studies have linked vST activation to dopaminergic gene variants (Camara et al., 2010; Dreher et al., 2009; Greer, Goldstein, Knutson, & Walker, 2016) and striatal dopamine release (Buckholtz et al., 2010; Dubol et al., 2018; Schott et al., 2008; Weiland et al., 2014, 2017). Recently, Dubol et al. (2018) showed a dimensional association between the dopamine transporter availability in the midbrain and activation within the vST across psychiatric disorders. In summary, the consistently reported transdiagnostic dopamine dysfunctions (Belujon & Grace, 2017; Fusar-Poli & Meyer-Lindenberg, 2013; Kapur, 2003) suggest that alterations in the dopamine system reflect a core mechanism underlying transdiagnostic reward processing dysfunctions (Dubol et al., 2018). However, the functional role of dopamine for these alterations is still insufficiently understood. The most compelling hypothesis links dopamine to inventive or motivational salience (Berridge & Robinson, 1998; Horvitz, 2000; Howes et al., 2020; Kapur, 2003; Martin-Soelch et al., 2001). Specifically, dopamine is conceptualized as a mediator transforming a neutral, irrelevant event into an attractive or aversive entity leading to the attribution of salience (Kapur, 2003). This association of stimuli (e.g., thoughts or cues) with reward subsequently influences the amount of attention or salience a stimulus gets, thereby driving action, inducing the feeling of hedonic subjective pleasure, influencing goal-

directed behavior and enabling the prediction of reward in the future (Kapur, 2003). According to this theory, psychosis is characterized by an dopaminergic overdrive which leads to a stimulus-independent release of dopamine and manifests in the aberrant assignment of salience (Kapur, 2003). In line, psychotic symptoms have consistently been linked to presynaptic striatal dopamine dysfunction, in particular elevated dopamine synthesis and release capacity (Howes, McCutcheon, Owen, & Murray, 2017). The genetic underpinnings of altered reward-related vST reactivity is more consistently reported for psychosis (see above), possibly indicating that aberrant salience is a core mechanism for psychosis. However, salience processing might also contribute to negative symptoms in a broader sense because reward-indicating stimuli elicit a diminished attribution of motivational salience which in turn prevents the feeling of pleasure and the engagement in enjoyable activities (Yuen et al., 2014) - a core symptom of affective disorders.

1.3.3 Beyond the vST: The hippocampal circuit as a mediator of aberrant salience and altered dopaminergic neurotransmission

So far, the reviewed studies and theories focused on vST function in isolation. However, the vST is part of several extended neural circuits (Báez-Mendoza & Schultz, 2013; Haber & Knutson, 2010). Moreover, psychiatric disorders, especially SZ, are thought to result from dysconnectivity syndromes rather than from localized neural defects (Cao, Dixson, et al., 2016; Meyer-Lindenberg, 2010). This calls for a more complex network perspective on brain function (Rasetti & Weinberger, 2011) but investigations of reward-related transdiagnostic circuit-level alterations are still limited.

In search for brain circuit candidates that might cause alterations in the dopamine system and result in the aberrant attribution of salience, a promising candidate is the hippocampus (see Kätzel, Wolff, Bygrave, & Bannerman, 2020 for a review). Substantial evidence implicates structural and functional hippocampal alterations in SZ and prodromal patients (Haukvik, Tamnes, Söderman, & Agartz, 2018; Heckers, 2001; Heckers & Konradi, 2015; Medoff, Holcomb, Lahti, & Tamminga, 2001; Roeske, Konradi, Heckers, & Lewis, 2020; Silbersweig et al., 1995; Stone et al., 2010) that have been related to positive and cognitive symptoms (Schobel et al., 2009; Tregellas et al., 2014) and linked to the pathological attribution of salience in SZ (Kätzel et al., 2020). Moreover, prominent animal models of SZ implicate neonatal lesions in the hippocampus in SZ-related behavioral alterations (Jones, Watson, & Fone, 2011) and showed that the connectivity between the hippocampus and prefrontal as well as striatal regions is disturbed (Lipska & Weinberger, 2002). Notably, Grace and colleagues (2016) postulated that impaired inhibitory

functioning of dopamine regulatory systems, centrally involving the hippocampus, lead to hyper-responsive dopamine levels in the vST (see Figure 1.3). Specifically, the nucleus accumbens and the ventral pallidum regulate the level of dopamine responsivity in the VTA to rapid, phasic events, like reward-related cues, by changing the proportion of dopamine neurons that are in an excitable state (Grace, 2012). This population activity of dopamine neurons is modulated by the hippocampus and dependent on the current context, for example a potentially rewarding environment (Belujon & Grace, 2015; Chergui et al., 1993; Grace & Bunney, 1984; Grace, 2010, 2012; Mayer, Westbrook, & Guthrie, 1984; Wolfram Schultz, 2016b). Specifically, this context-dependent regulation of tonic dopamine availability has been related to parvalbumin-expressing GABAergic interneurons in the ventral hippocampus (Grace, 2016). The consistently reported reductions of these inhibitory interneurons in mouse models of SZ (Lodge, Behrens, & Grace, 2009; Lodge & Grace, 2007) and post-mortem studies in SZ (Benes, Kwok, Vincent, & Todtenkopf, 1998; Zhang & Reynolds, 2002) are postulated to result in hyperactivity in the hippocampus which signals the nucleus accumbens to down-regulate the inhibitory dopamine system (see Figure 1.3; Grace, 2016). This causes stimuli to generate a maximal dopamine signal independent of their importance - the basis for aberrant salience (Grace, 2016). In line with these results, a recent review highlights the dopamine modulatory role of the hippocampus in the vST even suggesting it a novel circuit-level target for anti-psychotic action (Kätzel et al., 2020). However, neuroimaging studies in humans targeting the functional coupling between the vST and the hippocampus during reward processing are missing.

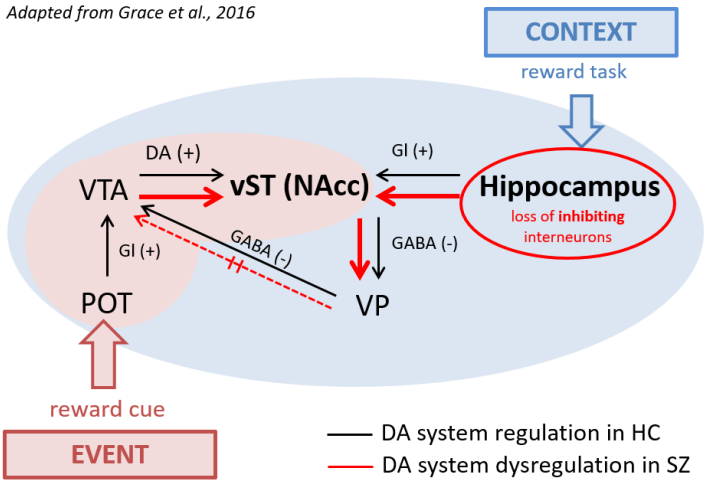

Figure 1.3: Dopamine (dys)regulation model outlined by Grace et al. (2016). SZ: schizophrenia, vST: ventral striatum, VTA: ventral tegmental area, POT: peduculopontine tegmentum, VP: ventral pallidum, DA: dopamine, Gl: glutamate, GABA: gamma-aminobutyric acid.

1.4 Imaging Methods

1.4.1 Brief introduction to functional magnetic resonance imaging (fMRI)

Within the following section, the basics of the fMRI methodologies are outlined. I will focus on the conceptually most important aspects, as a comprehensive introduction to the basic principles of fMRI is beyond the scope of this thesis and can be found for example in Ulmer & Jansen (2013).

Magnetic resonance imaging (MRI) is the most frequently used tool to acquire in-vivo brain images. It is non-invasive and exploits the magnetic properties of organic tissue using the nuclear magnetic resonance phenomenon. Specifically, the induction of a weak oscillating magnetic field with a specific frequency to atoms in a strong constant magnetic field disturbs the spin movement of the atoms. While this spin gradually recovers to its original spin direction along the static magnetic field, the duration of this recovery varies depending on the different brain tissues. These physical characteristics are used to create high dimensional structural brain images. Based on this, fMRI measures brain functioning by detecting the blood flow, defined as the blood-oxygenation-level-dependent (BOLD) signal. The BOLD response assesses the hemodynamic response which is induced by brain neural activity related to the energy used in active brain cells. Within the last 30 years fMRI has become one of the most frequently used tools in modern cognitive neuroscience (Singleton, 2009).

1.4.2 fMRI modalities: brain activation and functional connectivity

Functional activation

Traditionally, the main application of fMRI has been the identification of local brain activation differences between different task conditions and alterations thereof in a wide range of different populations (e.g., patient groups) or in association with relevant behavioral domains. Thereby, brain activation in response to a specific task condition compared to a control condition is assessed (e.g., monetary vs. neutral cues). Traditionally, task conditions are grouped in alternating blocks separating for example the monetary and neutral condition. Block designs are suited to detect single, slow and homogeneous overall brain responses to the respective task conditions. However, the presentation of trials in a randomized order reduces confounds such as stimulus predictability and allows the investigation of temporal characteristics of responses to varying stimulus categories (Chee, Venkatraman, Westphal, & Siong, 2003). These so called event-related designs are better suited for instrumental incentive delay tasks (Knutson, Westdorp, Kaiser, & Hommer,

2000). Briefly, trials are sorted post hoc, for example into the monetary and neutral condition and task regressors (e.g., cue win, cue neutral, target and feedback) are modeled as stick functions, convolved with the canonical hemodynamic response function (HRF) and entered into a first-level general linear model (GLM). Contrast beta images (e.g., win cue > neutral cue) are created that can then be subjected to group-level comparisons to assess differences in brain activation, such as vST reactivity to reward-indicating vs. neutral cues.

Functional connectivity

Given that most pathophysiological models of mental disorders rely on networks rather than localized neural defects (Cao, Dixson, et al., 2016), expanding analyses to functional interactions between neural circuits greatly increases the understanding of brain (patho-)physiology. This can be achieved by calculating the temporal covariance of BOLD signals between spatially distant brain regions (Friston, 1994). This has traditionally been applied during resting state but is also applicable for active fMRI tasks by adjusting for the task-related covariation between conditions. There are several ways to calculate connectivity between brain regions, for example seed-region correlation (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995), psycho-physiological interaction (PPI) analysis (Friston et al., 1997; O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012) and dynamic causal modelling (DCM) (Friston, Harrison, & Penny, 2003; Stephan et al., 2007). Most functional connectivity approaches are based on a priori defined regions of interest (ROI) from which fMRI time series are extracted. The most popular and straightforward approach is seed-based connectivity, which is based on correlation coefficients between the activity of the seed region and the activity at any other point in the brain (Friston, 2011). PPI expands the seeded connectivity approach by investigating interaction effects between the neural activity of the seed region (physiological variable) and the task conditions (psychological variable; Friston, 2011). However, PPI has been found to be less reliable compared to the seed-based connectivity approach, which is disadvantageous when dealing with patient populations and conducting imaging genetics studies (Bilek et al., 2013). In addition, correlational associations cannot infer causal interactions between brain regions, which can be accomplished by effective connectivity methods such as DCM. These approaches quantify the influence that one region exerts over another (Friston, 1994). The DCM approach has been shown to be more reliable compared to PPI (Schuyler, Ollinger, Oakes, Johnstone, & Davidson, 2010) but requires very specific hypotheses about a restrictive number of ROIs (or nodes). It is based on Bayesian model selection and allows to investigate how a specific brain region intrinsically influences another brain region and how this

coupling is influenced by the task conditions (Friston, Harrison, & Penny, 2003; Stephan et al., 2007). This allows to construct mechanistic models of brain function but is limited to a small number of brain areas, increasing the risk for spurious false-positive results (Schuyler et al., 2010) and prevents a more explorative whole-brain approach. While there is enormous progress in advancing functional connectivity methods (see Reid et al., 2019 for an overview), within the current work, we decided to supplement traditional activation analyses with seed-based connectivity analyses, taking into account the good reliability, efficiency and its suitability for an explorative brain-wide perspective.

1.4.3 Assessing reward processing with fMRI

Studying the neural systems underlying reward-related behaviors has generated a great amount of interest over the last decades. Thereby, the development of different reward paradigms enabled the investigation of different reward-related sub-processes.

The most widely used and validated paradigm is the *monetary incentive delay task* (MID) originally developed by Knutson and colleagues (2001). It is based on incentive conditioning paradigms in animal studies (Schultz et al., 1997) and breaks down reward processing into discrete stages of reward anticipation and reward consumption. Typically, the task requires a fast reaction to a target stimulus preceded by an incentive cue to win or to avoid losing an indicated reward (e.g., money). Incentive delay tasks have been adapted many times, varying for example the type of cues (win, lose, neutral) or the kind of reward (e.g., monetary, social, erotic pictures; see Lutz & Widmer, 2014 for a review).

However, incentive delay tasks rely on the successful completion of a reaction time task. Thereby, results might be confounded with deficits in response selection and execution, especially when comparing clinical populations with impaired cognitive performance abilities, like SZ (Dowd & Barch, 2012). Alternatively, *passive viewing tasks* present probabilistic rewards without any active behaviors. One example is the slot-machine task (Donkers, Nieuwenhuis, & Van Boxtel, 2005), where participants view three slot machines and are rewarded if the three pieces of fruit match. However, without behavioral and subjective measures it is unknown whether subjects understood the paradigm and engaged in the task equally well. In addition, in passive viewing paradigms subjects just consume the reward without having the possibility to influence the probability of receiving it, which reduces the engagement and personal significance of the task, thereby neglecting important aspects of reward processing.

More complex *decision making paradigms* like the monetary wheel of fortune task specifically focus on reward-related choices between options and the subsequent goal directed behaviors (Ernst et al., 2004). In contrast to incentive delay tasks, these paradigms involve a decision-making process including the weighting of magnitude and probability of potential gains or losses of competing options. They aim to study the neural basis of varying preferences among a range of probabilistic options. However, these tasks are cognitively demanding and involve complex information processing steps, resembled by a stronger recruitment of regions in the prefrontal cortex (Ernst & Paulus, 2005). Within the current thesis, we specifically wanted to study transdiagnostic reward-related vST brain activation and system-level connectivity patterns. Therefore, we decided to use the MID task as it has been proven a reliable (Grimm et al., 2014) and efficient way to capture reward anticipation throughout psychiatric disorders.

1.5 Research Questions and Hypothesis

Overall, the reviewed studies highlight reward anticipation alterations in a range of psychiatric disorders, including SZ, BP, MD and ASD. However, while the literature is still dominated by disorder-specific mechanistic theories, transdiagnostic studies are needed to assess dimensional brain-behavior relationships and test disorder-specificity for genetic underpinnings and biological mechanisms underlying reward-related alterations. Specifically, the hippocampus has been found to modulate dopamine release in the vST and its functional interaction with the reward system might shed light into the biological basis of aberrant salience processing during psychotic episodes. Based on this theoretical background the following research questions and hypothesis were derived. Please note that several parts of this thesis have already been published (Study 1: Schwarz et al., 2019) or are about to be published (Study 2: Schwarz et al., in review) by the doctoral candidate as a first author. Therefore, certain sections, tables, or figures of this thesis will be identical to these publications.

Research Question 1 (Study 1 and 2): Are there *categorical* group differences in vST activation during reward anticipation between healthy control (HC) and patient groups in the extended moods-psychosis spectrum?

> *Hypothesis 1:* Compared to HC, vST activation during reward anticipation is reduced in patients with SZ (*hypothesis 1.1*), BP (*hypothesis 1.2*), MD (*hypothesis 1.3*) and ASD (*hypothesis 1.4*), respectively.

Research Question 2 (Study 1): Is the activation of the vST during reward anticipation related to transdiagnostic *dimensional* measures of neurocognitive function?

Hypothesis 2: Transdiagnostic vST alterations relate to dimensional measures covering affective (*hypothesis 2.1*), cognitive (*hypothesis 2.2*) and social (*hypothesis 2.3*) functioning. *Explorative hypothesis 2.4:* Are dimensional measures of basic neurocognitive functions associated with neural networks beyond the vST?

Research Question 3 (Study 2): Do alterations in the functional coupling between the vST and the hippocampus qualify as a new connectivity endophenotype for altered reward processing in psychotic disorders.

Hypothesis 3.1: Activation of the reward system induces an overall reduction of functional connectivity between the vST and the hippocampus specifically in psychotic disorders.

Hypothesis 3.2: Functional vST-hippocampus coupling 1) is reduced in first-grade relatives with psychotic but not mood disorders and 2) relates to polygenic risk scores for SZ in HC.

Hypothesis 3.3: Functional vST-hippocampus coupling is associated with behavioral dimensions of positive (*hypothesis 3.1*) but not negative (*hypothesis 3.2*) or cognitive (*hypothesis 3.3*) symptoms.

2 EMPIRICIAL STUDIES

2.1 Study 1 – Transdiagnostic prediction of affective, cognitive and social function through brain reward anticipation in schizophrenia, bipolar disorder, major depression and autism spectrum diagnoses[1]

2.1.1 Abstract

Background: The relationship between transdiagnostic, dimensional and categorical approaches to psychiatric nosology is under intense debate. To inform this discussion, we studied neural systems linked to reward anticipation across a range of disorders and behavioral dimensions.

Methods: We assessed brain responses to reward expectancy in a large sample of 221 participants including patients with schizophrenia (N = 27), bipolar disorder (N = 28), major depressive disorder (N = 31), autism spectrum disorder (N = 25), and healthy controls (N = 110). We also characterized all subjects with an extensive test battery from which a cognitive, affective and social functioning factor was constructed. These factors were subsequently related to functional responses in the vST and neural networks linked to it.

Results: We found that blunted vST responses were present in schizophrenia, bipolar disorder and autism spectrum disorder, but not in major depression. Activation within the vST predicted individual differences in affective, cognitive and social functioning across diagnostic boundaries. Network alterations extended beyond the reward network to include regions implicated in executive control. We further confirmed the robustness of our results in various control analyses.

Conclusion: Our findings suggest that altered brain responses during reward anticipation show transdiagnostic alterations that can be mapped onto dimensional measures of functioning. They also highlight the role of executive control of reward and salience signaling in the disorders we study and show the power of systems-level neuroscience to account for clinically relevant behaviors.

[1] **Published as**: Schwarz K.*, Moessnang C.*, Schweiger J.I., Baumeister S., Plichta M.M., Brandeis D., Banaschewski T., Wackerhagen C., Erk S., Walter H., Tost H., Meyer-Lindenberg A. Transdiagnostic Prediction of Affective, Cognitive, and Social Function Through Brain Reward Anticipation in Schizophrenia, Bipolar Disorder, Major Depression, and Autism Spectrum Diagnoses. *Schizophr Bull*. 2019; 46(3): 592-602.

2.1.2 Introduction

Alterations in reward sensitivity or reinforcement-dependent learning play a key role in psychiatric disorders. Previous research has focused on SZ where altered brain responses during the anticipation of reward, in particular in the vST, are well-established (Radua et al., 2015). However, a growing number of studies reported network alterations during reward anticipation in other disorders (Arrondo et al., 2015; Hägele et al., 2015; Whitton, Treadway, & Pizzagalli, 2015) including MD (Keren et al., 2018; Zhang et al., 2013), BP (Nusslock et al., 2012) and ASD (Dichter, Felder, et al., 2012), mirroring the significant overlap between these disorders in symptomatology and genetic risk architecture (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). In this sense, reward anticipation is a prime example of the current discussion whether categorical diagnoses should be supplemented, or even supplanted, by dimensional constructs linked to function.

Accordingly, recent studies have associated striatal brain responses during reward anticipation to dimensional concepts like anhedonia, depressive symptom severity or psychotic symptoms across psychiatric conditions (Arrondo et al., 2015; Hägele et al., 2015; Nielsen et al., 2012; Satterthwaite et al., 2015). These approaches highlight the potential of neuroimaging biomarkers in explaining brain-behavior relationships in a more dimensional and inclusive way, i.e., by means of shared psychological or symptom domains and beyond traditional definitions of health and disease (Cuthbert, 2014; Insel et al., 2010). If established, such markers would allow the investigation of brain-behavior relationships independent of clinical status and diagnostic entity, thereby enhancing our current categorical understanding of mental disorders and their neurobiological representation to a more dimensional framework, from which valuable clues for therapy research may arise.

Building on these recent approaches, we investigated the transdiagnostic relevance of reward signaling in two ways. First, while previous studies of this system have usually investigated single behavioral domains in restricted groups of disorders, we performed a broad (neuro)psychological characterization to generate independent, data-driven factors that converge on underlying traits or states in a range of participants with serious mental illness along the moods-psychosis spectrum (SZ, BP, MD, ASD). While exploratory in nature, these factors were expected to map on cognitive, affective and social functioning, given our selection of tests and questionnaires. Second, previous research oftentimes studied the vST in isolation, often combined with disorder-specific

hypotheses about underlying mechanisms (e.g., dopamine hypothesis of SZ (Howes & Kapur, 2009)). However, it is clear that the vST participates in several extended networks or loops linked to a range of cognitive, affective and social behaviors (Báez-Mendoza & Schultz, 2013; Haber & Knutson, 2010). Alterations on the circuit-level can be studied using functional connectivity, which examines correlations in activity across regions. To date, several studies have reported alterations in cortico-striatal connectivity in SZ (e.g., Tu et al., 2012) and other diagnostic entities (e.g., BP (Vargas, López-Jaramillo, & Vieta, 2013), MD (Fischer, Keller, & Etkin, 2016), ASD (Delmonte, Gallagher, O'Hanlon, McGrath, & Balsters, 2013). However, their joint interpretation is hampered by methodological differences (e.g., resting-state versus task-based fMRI) and transdiagnostic research on brain-behavior relationships is scarce (e.g., Sharma et al., 2017). Accordingly, we aimed to identify reward-related alterations in distributed neural networks linked to the vST between and across diagnostic categories. We expected reward-related functional alterations to involve brain circuits beyond the vST. We also expected a relationship of transdiagnostic alterations with dimensional measures, based on evidence of an association with affective measures (Arrondo et al., 2015; Hägele et al., 2015), the relevance of cognitive control for the processing of motivationally relevant cues (Cole, Repovš, & Anticevic, 2014), and the inherently motivational salience of social stimuli (Chevallier et al., 2012).

In addition, we anticipated experimental challenges that arise in clinical imaging research, in particular when investigating different patient groups in the same study. We therefore carefully considered various factors related to clinical characteristics (Greene, Black, & Schlaggar, 2016) (e.g., comorbidities, medication) and data quality issues (e.g., motion artifacts, test-retest reliability) in several control analyses.

2.1.3 Methods

Sample

This study recruited a prospective new sample of 279 subjects. All individuals provided written informed consent for a study protocol approved by the institutional review board of the Medical Faculty Mannheim. After quality assurance procedures, the final sample included 221 participants (N_{SZ} = 27, N_{BP} = 28, N_{MD} = 31, N_{ASD} = 25, N_{HC} = 110; see Table 2.1).

Table 2.1: Sample description.

Group	HC	SZ	BP	MD	ASD	Between-group differences
N	110	27	28	31	25	
Age	30.4 (10.3)	32.4 (10.4)	34.0 (9.6)	35.2 (11.2)	32.1 (9.6)	$F_{(4,216)} = 2.12$, $p = .080$
Sex (m/f)	54/56	18/9	12/16	8/23	14/11	$\chi^2_{(4)} = 10.98$, $p = .027$
Education (years)	12.4 (1.1)	11.1 (1.9)	12.3 (1.2)	11.7 (1.5)	11.9 (1.5)	$F_{(4,216)} = 5.55$, $p = < .001$
Frame-wise Displacement	0.2 (0.06)	0.2 (0.06)	0.2 (0.07)	0.2 (0.08)	0.2 (0.06)	$F_{(4,216)} = 1.56$, $p = .185$
Medication value	-	2.8 (2.4)	2.6 (1.3)	1.7 (1.5)	0.4 (0.8)	$F_{(3,107)} = 11.98$, $p = < .001$
CPZ-e	-	415.0 (45.2)	123.8 (42.7)	16.7 (41.3)	3.3 (47.1)	$F_{(3,102)} = 13.66$, $p < .001$
CGI	-	4.35 (1.2)	3.46 (1.2)	3.75 (1.1)	3.5 (1.1)	$F_{(3,100)} = 3.36$, $p = .022$
PANSS	-	54.6 (16.5)	41.0 (10.2)	46.5 (9.1)	-	$F_{(2,82)} = 8.27$, $p = .001$
HAM-D	-	7.8 (5.5)	8.0 (6.5)	13.2 (6.0)	-	$F_{(2,82)} = 7.64$, $p = .001$
YMRS	-	1.2 (2.4)	2.8 (3.7)	0.6 (1.2)	-	$F_{(2,82)} = 5.37$, $p = .006$
ADOS	-	-	-	-	9.5 (2.8)	
Reaction time (sec)	239.9 (27.2)	238.3 (28.5)	242.5 (51.8)	244.9 (28.1)	253.3 (29.9)	$F_{(4,216)} = 1.06$, $p = .146$
Number of win trials (max 15)	10.3 (1.1)	10.3 (1.5)	10.0 (1.3)	10.5 (1.1)	9.8 (1.2)	$F_{(4,216)} = 1.72$, $p = .380$

Displayed are mean values (standard deviation) or numbers (male/female) and statistical between-group comparisons. For nonparametric test, we used the Kruskal-Wallis test (df = 5). For parametric tests, analysis of variance was computed. Abbreviations: HC: healthy control; SZ: schizophrenia; BP: bipolar disorder, MD: major depression; ASD: autism spectrum disorder; m: male; f: female; CPZ-e: chlorpromazine dose equivalents CGI: Clinical Global Impression Scale (Guy, 1976) (1: no mental disorder – 7: extreme mental disorder); PANSS: Positive and Negative Symptom Rating Scale (Kay, Fiszbein, & Opler, 1987); HAMD-D: Hamilton Depression Scale (Hamilton, 1967); YMRS: Young Mania Rating Scale (Young, Biggs, Ziegler, & Meyer, 1978); ADOS: Autism Observation Schedule Module 4 (Lord, Rutter, DiLavore, & Risi, 1999).

Diagnostic evaluation: Patients were recruited from in- and outpatient treatment facilities. Healthy subjects were recruited from the local community by advertisement. Psychiatric diagnoses were confirmed by trained clinical interviewers using the Structured Clinical Interview

for DSM-IV-TR axis I disorders (SCID-I) (First, Spitzer, Gibbon, & Williams, 2001) for all patient groups and the Autism Diagnostic Observation Schedule Module 4 (ADOS-G) (Lord et al., 1999) for ASD patients. Patients with BP type 2 were excluded.

Symptom severity: Current symptom severity was assessed in patients with episodic disorders (MD, SZ, BP) using the Positive and Negative Symptom Scale (PANSS, Kay, Fiszbein, & Opler, 1987), the Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978) and the Hamilton Depression Scale (HAM-D) (Hamilton, 1967). In ASD, we assessed total scores in the Autism Diagnostic Observation Schedule Module 4 (Lord et al., 1999) in order to estimate disorder severity. In addition, general disorder severity was rated using the Clinical Global Impression Scale (CGI) (Guy, 1976) across all patients (see Table 2.1). In the control group, participants reporting a personal or family history of psychiatric disorders using the SCID-I screening (First et al., 2001) were excluded.

Comorbidities: As nearly half of the patients with psychiatric disorders fulfill the criteria of at least one more mental disorder (Kessler et al., 2005), we followed the recommendations of Greene et al. (2016) to not strictly exclude patients with a lifetime or concurrent comorbid psychiatric diagnosis (see Table S2.1). However, patients were only included if comorbidities 1) evolved as a consequence of, or 2) were markedly less pronounced as the primary disorder, as evaluated in the clinical interview. In addition, patients reporting a lifetime diagnosis of substance dependence or personality disorder were excluded. The main reason to exclude patients with profound axis II disorders was because by definition, axis II disorders evolve early in life (First et al., 2001) and rather aggravate or even cause axis I disorders instead of evolving as a consequence of axis I disorders (Links & Eynan, 2013). Regarding substance dependence, a lifetime diagnosis has been associated with alterations in the mesolimbic reward network during reward anticipation (Luijten, Schellekens, Kühn, Machielse, & Sescousse, 2017), which is a major confound in the current investigation.

Exclusion criteria: None of the subjects reported any history of neurological or significant general medical problems including liver, cardiac, or renal dysfunctions, a history of head trauma or pregnancy.

Quality assurance procedures

Head motion parameters were quantified as previously detailed (Grimm et al., 2014; Plichta et al., 2012; Yan et al., 2013) and included the maximal volume-to-volume translational excursions

across the time series, the maximal volume-to-volume rotational excursions across the time series, and the mean voxel-based frame-wise displacement (mFD) (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). The signal-to-noise, signal-to-fluctuation and signal-to-ghost ratio of images was calculated using the New York University Center for Brain Imaging data Quality toolbox (Friedman & Glover, 2006; Simmons, Moore, & Williams, 1999; Weisskoff, 1996). Statistical comparisons of data quality parameters between the groups were performed with SPSS (IBM, SPSS, version 23) using univariate Analyses of Covariance (ANCOVA), including diagnosis as factor of interest and age, sex as well as educational level as covariates of no interest. While groups differed in most of the quality parameters in the initial sample, these differences were balanced when excluding subjects with more than 20% of frames exceeding 0.5 mm frame-wise displacement (FD) (see Table S2.2). As expected (Greene et al., 2016), this led to the exclusion of a higher proportion of patient than control data sets. However, we deemed this strategy absolutely necessary since it allowed for an effective image quality control (QC) (i.e., no between-group differences in mFD, translation, rotation, and signal-to-noise ratios), thereby minimizing the risk for spurious findings, and still ensured sufficient numbers across group.

(Neuro)Psychological characterization

Testing was performed by trained examiners using a battery of well-established tests for intellectual abilities including reasoning, attention, verbal fluency, episodic memory, and working memory. Affective state and trait measures, questionnaires on personality characteristics and social functioning were acquired by online questionnaires (see Table S2.3 for all Measures and subscales included in the analysis). We performed a principal component analysis (PCA) in order to identify underlying independent components or factors that reflect higher-order dimensions of (neuro)psychological functioning. We first tested whether our questionnaire and neuropsychological test data was suitable to perform PCA (Streiner, 1994). In a first step, individual data were checked for completeness and missing values (less than 5%) were imputed using the mean of the remaining values. We then computed the Kaiser-Meyer-Olkin measure of sampling adequacy. The resulting value of 0.89 was well above the commonly recommended minimum value of 0.6. In addition, we computed the Bartlett's test of sphericity which indicated that included variables differed sufficiently from each other ($\chi^2_{(496)} = 42.037$, $p < .001$). Subsequently, PCA was applied to identify underlying patterns of coherence among the included variables. The factor analysis resulted in seven variables with an eigenvalue greater than 1. Following the Scree test (Figure S2.1), we extracted three factors that explained more than 50% of the variance in the

data. Finally, we applied varimax rotation in order to simplify the interpretation of the factors. Commonalities and factor loadings of all included measures and subscales are outlined in Table S2.3.

Neuroimaging paradigm

We used an adapted version of a well-established event-related incentive delay task involving monetary (Kirsch et al., 2003; Knutson et al., 2001) and social (Spreckelmeyer et al., 2009) reward during fMRI and two conditions (win cue, neutral cue; see Figure 2.1). Subjects were asked to give a speeded response (button press) to a visual target (brief light flash) presented on a screen. An arrow pointing upwards indicated the possibility to obtain a reward if responses were given within a predefined response time window (win trial). No reward option was given in trials preceded by a sideways arrow (neutral trial). The response time window was continuously adapted to ensure a comparable number of reward events across subjects and groups (~60 %). Sufficiently fast responses on win trials were followed by the presentation of a 2€ coin in the monetary reward task and a smiling female face in the social reward task as feedback. Blurred control stimuli were presented in neutral trials and as feedback following slow responses in win trials. In total, 30 win trials and 30 neutral trials were presented in a pseudorandomized order. We did not differentiate between reward types based on previous evidence of overlapping neural substrates (Lin, Adolphs, & Rangel, 2012), which we similarly demonstrate in our control analyses (see below). No group differences in the mean reaction time or mean outcome (i.e., number of win trials) were detected, respectively (see Table 2.1). This suggests that all subjects understood the paradigm and engaged in the task equally well.

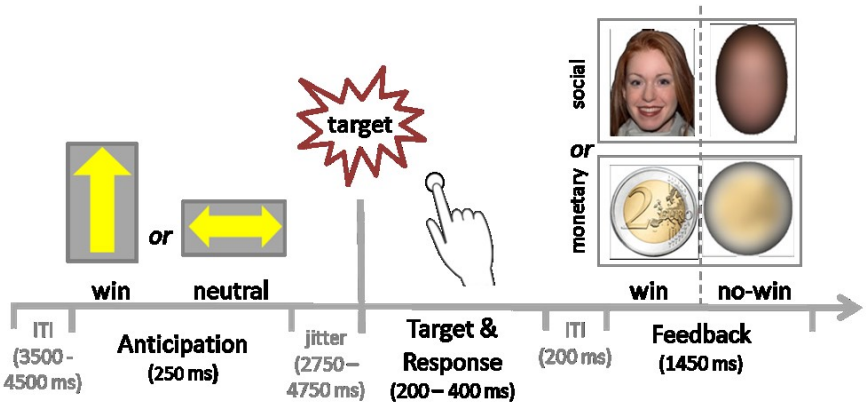

Figure 2.1: Reward anticipation task. Subjects were asked to give speeded responses to a visual target (brief light flash). Preceding cues indicated whether subjects have the chance to win 2 Euros (monetary condition) or Julia's smile (social condition) if the response is fast enough. Note that reward types were presented in two separate sessions which were combined during data analysis. ITI: inter trial interval.

MRI data acquisition and preprocessing

Magnetic resonance imaging was performed on a 3-T scanner (Siemens Trio) equipped with a 12-channel head coil. Functional images were acquired using an echo-planar imaging (EPI) sequence (TE: 30 ms, TR: 2 s, α: 80°, matrix: 64 × 64, field of view (FOV): 192 × 192 mm, in-plane resolution: 3 x 3 mm, slice thickness: 4 mm, gap: 1 mm, 28 axial slices, 332 volumes). Image preprocessing followed standard processing routines in SPM12 (Wellcome Centre for Human Neuroimaging, n.d.), including a two-pass realignment procedure, slice time correction, registration of the functional mean image to the Montreal Neurological Institute (MNI) template and spatial normalization into standard stereotactic space, application of resulting normalization parameters to the functional time series, resampling to 3 mm isotropic voxels, and smoothing with an 8 mm full-width at half-maximum Gaussian Kernel. Datasets with more than 20 % of frames exceeding 0.5 mm FD were excluded.

First-level analyses

Activation analyses: Functional activation during reward anticipation was assessed as differential response to win cues as compared to neutral cues. To this end, the four task regressors (cue win, cue neutral, target and feedback) were modeled as stick functions, convolved with a canonical HRF, and entered into a first-level GLM, along with six session-wise motion regressors derived from the realignment step. At the model estimation stage, a high-pass filter with a cutoff of 128 seconds and an autoregressive model of the first order were applied. Contrast images (win cue > neutral cue) were created and subjected to second-level statistical analysis.

Connectivity analyses: We assessed functional connectivity of the vST using a seeded connectivity approach. For each subject, we extracted the first eigenvariate of the time series in the right vST using a 6mm-sphere centered at the peak voxel of the main effect of group [x = 12, y = 8, z = -10]. We decided to investigate vST connectivity of the right hemisphere, as the task and group effect in the right vST was stronger compared to the left. The time series was adjusted for effects of interest (i.e., removal of nuisance variables) and subjected to first-level GLMs, along with the following regressors of no interest: (1) movement parameters from the realignment step, (2) first eigenvariates derived from cerebral spinal fluid and white matter masks and (3) regressors encoding for the experimental conditions. Model estimation was performed as outlined above. The resulting beta image was subjected to second-level analyses.

Second-level analyses

ROI definition: In line with our hypothesis of aberrant vST activation (Hägele et al., 2015), significance for the incentive delay task was defined as $p < 0.05$, family-wise error (FWE) corrected within a well-established a-priori defined mask of the vST (Plichta et al., 2012), which was composed of the "caudate head" taken from the WFU-PickAtlas (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003) and the "accumbens" mask from the Harvard-Oxford Subcortical Structural Atlas (Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006).

Categorical between-group analyses: To study reward network (dys)function between diagnostic entities, we conducted categorical analyses using individual contrast images for activation and functional connectivity and full-factorial designs with diagnostic group (HC, SZ, BP, MD, ASD) as between-subject factor. As groups were naturally heterogeneous with respect to age, sex and educational level, we included these variables as covariates of no interest in all analyses. In addition, despite non-significant differences in head motion between groups (see Table 2.1), we included mFD (Power et al., 2012) as covariate of no interest across analyses. In case of a significant main effect of group, F-tests were followed up by post-hoc t-tests for group comparisons. Significance was assessed at the voxel-level and defined *a priori* as $p < .05$, FWE-corrected within the predefined mask of the vST. Outside this mask, voxel-level significance was defined as $p_{FWE} < .05$, corrected across the whole brain.

Dimensional analyses: We further investigated whether inter-individual differences in behavior can be mapped onto reward network functioning irrespective of diagnostic status. We performed a principal component analysis implemented in SPSS (IBM, SPSS, version 23) to identify independent components or factors reflecting higher-order dimensions of (neuro)psychological functioning. The resulting factors could be mapped onto dimensions of cognitive, affective, and social functioning. To identify associations of factors with functional brain responses, we first included individual factor loadings as covariates of interest in one-sample t-tests on brain activation and connectivity along with the above-named covariates of no interest, without controlling for group. The same statistical thresholds were applied as outlined above. A second analysis step was performed for our vST ROI to test whether individual factor loadings were predictive of neural responses beyond the effect of diagnostic category. We extracted peak-voxel estimates within significant activation clusters identified in the previous analysis step and used these measures as dependent variables in post-hoc multiple regression analyses. We converted

the variable coding for the five diagnostic groups into four dichotomous dummy variables using the HC group as the reference category. The same was done for the variable coding for the interaction effect (group X dimension). We included the resulting variables together with the dimensional factors and our covariates of no interest as independent variables into the regression model.

Control analyses and reliability study

In order to address the challenges common to clinical imaging, we tested the robustness of the identified reward-related activation and connectivity phenotypes in various control analyses.

Medication: The included patients were medicated which is known to influence reward network functioning (Abler, Erk, & Walter, 2007; Stoy et al., 2012). In order to target the potentially confounding effect of antipsychotic medication, we computed chlorpromazine dose equivalents (CPZ-e). We used the mean effective daily dose (ED50) for CPZ-e to distinguish between high and low dosage. However, as CPZ-e values don't take into account other classes of medication, we additionally calculated a standardized composite medication value following an established procedure for clinical studies that deal with different types of medication (Hassel et al., 2008). In short, for every substance we coded the dosage as absent = 0, low = 1, or high = 2 and computed a sum score for all substances taken by an individual. Antidepressants and mood stabilizers were coded as high vs. low dosage based on the rating scores published by Sackeim (2001). The resulting composite scores and CPZ-e values (see Table 2.1 and Table S2.1) were subsequently related to second-level peak voxel estimates using partial correlation analyses in SPSS (IBM, SPSS, version 23) while controlling for age, sex, and education.

Motion: The motion control strategies performed for functional connectivity analyses were fourfold: First, we included the six motion regressors extracted from image realignment in the individual first level models. Second, we included the first eigenvariates derived from cerebral spinal fluid and white matter masks in the individual first level models. Third, we included mFD as covariate of no interest across all group-level analyses. Forth, we performed additional control analyses to further follow up on the potential influence of motion on the identified phenotypes. In these control analyses, we performed partial correlation analyses on identified peak voxel estimates and mFD values while controlling for age, sex and education.

Monetary vs. Social Reward: In order to investigate the effects of reward type (monetary vs. social), we performed additional categorical and dimensional second-level analyses as outlined

above using individual contrast images capturing the interaction effect between condition and reward type (contrast: (win [social] > neutral [social]) > (neutral [monetary] > win [monetary]).

Effect of current depressive state: In order to test whether group differences in vST activation were robust to differences in current depressive state, we included depression severity (not depressed, mildly depressed, moderately depressed, severely depressed) as assessed by the Beck Depression Inventory (BDI) (Hautzinger et al., 1995) as a nuisance variable in the second-level GLM on group differences while controlling for age, sex, education and mFD. We similarly explored whether identified peak voxel estimates reflecting group differences and dimensional associations were robust to the inclusion of current depressive state as a nuisance variable using ANCOVA analyses along with the same covariates of no interest. Finally, we tested whether mean vST activation in MD patients was associated with current depressive state while controlling for sex, age, education and mFD.

Exploring sex effects: In order to further follow up on possible sex effects we specifically looked at sex effects and the interaction between diagnostic group and sex using ANCOVA.

Reward feedback: Functional activation during reward feedback was assessed as differential response to feedback (fb) during win and during neutral trials. Fb during win trials consisted either of the presentation of the reward (successful trial) or the presentation of the blurred image of the reward (unsuccessful trial). For first-level analysis, the six task regressors (cue win, cue neutral, target, fb win (successful, not successful) and fb neutral) were modeled as stick functions, convolved with a canonical HRF, and entered into a first-level GLM, along with six session-wise motion regressors derived from the realignment step. At the model estimation stage, a high-pass filter with a cutoff of 128 seconds and an autoregressive model of the first order were applied. Contrast images (fb win > fb neutral) were created and subjected to second-level statistical analysis.

To study reward network (dys)function between diagnostic entities, we conducted categorical analyses using the individual contrast images and full-factorial designs with diagnostic group (HC, SZ, BP, MD, ASD) as between-subject factor and age, sex, educational level and frame-wise displacement (Power et al., 2012) as covariates of no interest. We first calculated the main effect of task (fb win > fb neutral). In order to explore categorical group differences, we then calculated the main effect of group. In case of a significant main effect of group, F-tests were followed up by post-hoc t-tests for group comparisons. We also performed dimensional analyses following the

same analysis rationale as outlined in the manuscript. Again, significance was defined *a priori* as $p < .05$, FWE-corrected within a well-established mask of the vST (Plichta et al., 2012) (see above). Outside this mask, significance was defined as $p_{FWE} < .05$, corrected across the whole brain on the voxel-level.

Test-Retest analyses: Test-retest reliability is an important quality measure for neuroimaging phenotypes. To further probe and establish the value of the identified transdiagnostic activation and connectivity markers for future therapy studies we conducted a test-retest reliability study in 28 healthy volunteers (mean age: 22.9 ± 2.8 years, 14 females) scanned twice with the same fMRI paradigm within 3 consecutive weeks (mean time interval: 15.8 ± 3.5 days). Exclusion criteria included a lifetime history of neurological or psychiatric disorder, current intake of psychoactive substances, significant general medical problems including liver, cardiac, or renal dysfunctions, a history of head trauma, and pregnancy. All individuals provided written informed consent for a study protocol that was approved by the institutional review board of the Medical Faculty Mannheim. Data processing analyses followed the same procedures outlined above. Voxel-wise intra-class correlation coefficients (ICCs) were calculated to quantify relative consistency between sessions (Bilek et al., 2013; Cao, Bertolino, et al., 2016; Moessnang et al., 2016; Plichta et al., 2012; Shrout & Fleiss, 1979). The median ICC was calculated across voxels for the whole brain and the vST mask. Reliability was defined as fair for ICCs > 0.40, and as good for ICCs > 0.59 (Shrout & Fleiss, 1979).

2.1.4 Results

Categorical analyses: differential activation and vST-connectivity during reward processing

Compared to HC, we observed reduced vST activation during reward anticipation in SZ, BP and ASD ($p_{FWE} < .05$, small volume correction (SVC)), but not MD (see Figure 2.2 and Table 2.2). The post-hoc comparison of groups revealed that the reduction in striatal activation was driven by the comparison between the HC group and three patient groups (SZ, BP and ASD). In addition, the MD group showed significantly stronger striatal activation compared to the BP group (see Table S2.4).

Beyond the vST, activation analyses revealed group differences in areas that have previously been linked to the executive control network, such as the inferior parietal lobule (IPL) and lateral prefrontal cortex ($p_{FWE} < .05$, whole-brain corrected; see Figure 2.3a, Table 2.2). Post-hoc tests revealed that these effects were most pronounced in BP compared to HC (see Table 2.2 and Table S2.5). In addition, we detected group differences in vST connectivity with the IPL and

cerebellum (p_{FWE} < .05, whole-brain corrected, see Figure 2.3b, Table 2.2) which were mainly driven by reduced functional connectivity in SZ and BP compared to HC (p_{FWE} < .05, whole-brain corrected, see Table 2.2 and Table S2.5).

Table 2.2: Categorical group differences.

Region	k	x	y	Z	F/T	p_{corr}	Significant post-hoc group differences
Activation							
ventral striatum R*	69	12	8	-10	7.39	.001	HC > SZ, HC > BP, HC > ASD, MD > BP
ventral striatum L*	15	-12	5	-10	5.86	.009	HC > BP, HC > ASD
inferior parietal lobule L [IPC (PGa)]	32	-39	-61	53	9.45	.007	HC > BP
inferior parietal lobule R [IPC (PGp)]	23	33	-73	44	8.88	.017	HC > BP
lateral frontal gyrus R [Area 45]	10	60	23	8	8.57	.026	HC > BP
vST - Connectivity							
inferior parietal lobule R [SPL (7A)]	43	33	-58	53	12.61	< .001	HC > SZ, HC > BP
fusiform L	34	-24	-70	-16	10.66	.002	HC > BP
cerebellum R	19	24	-37	-37	9.56	.011	HC > SZ

Cluster extent *k* is given at p_{corr} < .05, family wise error corrected for multiple comparisons within the whole brain for k > 10 voxels or within the *ventral striatum region of interest using small volume correction. X-, y-, and z-coordinates (MNI) and statistical information refer to the peak voxel(s) in the corresponding cluster (voxel-level statistics). R: right, L: left.

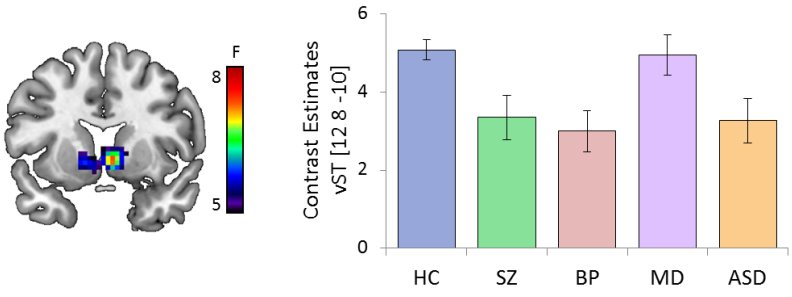

Figure 2.2: Categorical group differences in vST brain responses. vST reactivity during reward anticipation (cue win vs. neutral) and plotted contrast estimates (mean, SE) of the right vST. HC: healthy control, SZ: schizophrenia, BP: bipolar disorder, MD: major depression, ASD: autism spectrum disorder, vST: ventral striatum. For illustration, a significance threshold of p_{uncorr} < .001 was applied.

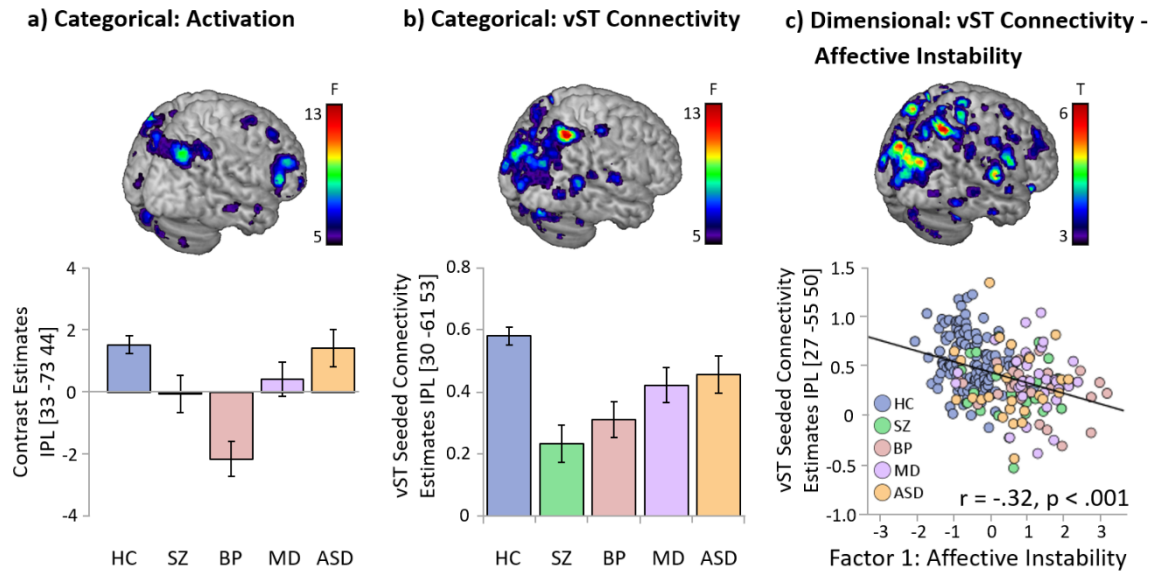

Figure 2.3: Whole brain activation and connectivity results. Main effect of group for activation (a; cue win vs. neutral) and ventral striatal (vST) seeded connectivity (b). c) Negative association between affective instability and vST seeded connectivity with the right inferior parietal lobule (IPL). Bar plots depict respective contrast and seeded connectivity estimates (mean, SE) of the peak voxel in the right IPL. *r*: Pearson correlation coefficient, HC: healthy control, SZ: schizophrenia, BP: bipolar disorder, MD: major depression, ASD: autism spectrum disorder. For illustration, a significance threshold of $p_{uncorr} < .001$ (cluster extent > 20) was applied.

Dimensional analyses: transdiagnostic associations between activation and vST-connectivity during reward processing

Extraction of dimensional measures: The factor-analytical approach revealed three uncorrelated factors covering aspects of affective, cognitive, and social functioning (see Figure 2.4a). We refer to the first factor as *affective instability* since it is composed of diverse psychological constructs like anxiety, anhedonia, neuroticism, self-control, or impulsivity, all of which converge on difficulties to adequately regulate the affective state. Consistent with this label, patients with MD and BP showed higher factor loadings compared to the remaining groups (factor 1: $F_{(4,219)} = 54.104$, $p < .001$). The second factor includes different measures assessing neurocognitive performance (e.g., memory, reasoning) and is referred to as *cognitive functioning*. In line with previous studies (Vöhringer et al., 2013), patients with SZ showed lower factor loadings compared to all other groups. In addition, patients with BP revealed lower values compared to HC, whereas no differences between the remaining groups were detected ($F_{(4,219)} = 4.417$, $p < .01$). The third factor specifically covers measures related to social traits and is referred to as *social functioning.* As expected, patients with ASD showed lower factor loadings compared to all other groups

($F_{(4,219)}$ = 36.861, p < .001). Despite the existence of mean group differences, both within-group variance and cross-group overlap suggest a broad distribution of each factor across disorders (see Figure 2.4a).

Association of dimensional measures with brain activity and connectivity: Higher affective instability (factor 1) was associated with reduced vST activation, while higher cognitive and social functioning (factor 2 and 3) was related to higher vST activation (p_{FWE} < .05, SVC, Figure 2.4b, Table 2.3). On the whole-brain level, higher affective instability (factor 1) was associated with lower activation in lateral and medial frontal areas as well as in the cerebellum (p_{FWE} < .05, whole-brain corrected, Table 2.3). No significant association emerged for factors 2 and 3. In addition, affective instability (factor 1) was associated with reduced vST-connectivity with visual and motor areas and in parietal regions, with prominent clusters in the IPL, insula, and putamen (see Figure 2.3c, Table 2.3).

Post hoc analyses of dimensional measures: Post-hoc multiple regression analyses revealed that individual factor loadings predicted vST activation beyond the effect of diagnostic group for affective instability and cognitive functioning, while the association with social functioning was trend-level significant (see Figure 2.4c and the following section for details).

Factor 1 (affective instability): Multiple regression analyses indicated that the above outlined predictors explained 17.3 % of the total variance in the right vST (R^2 = .173; $F_{(12,208)}$ = 3.619, p <.001) and 16.4 % of the total variance in the left vST (R^2 = .164; $F_{(12,208)}$ = 3.395, p < .001). For the right vST, only factor 1 (beta = -1.687, p = .044) and age (beta = -.087, p = .007) predicted activation, whereas for the left vST, diagnostic group (BP vs. HC: beta = -3.077, p = .024) and age (beta = -.095, p = .002) but not the dimensional factor (beta = -.616, p = .431) reached statistical significance. None of the other above named regressors including all interaction terms reached significance (all p > .05).

Factor 2 (cognitive functioning): Multiple regression analyses indicated that the above outlined predictors explained 17.7 % of the total variance in the right vST (R^2 = .177; $F_{(12,208)}$ = 3.713, p < .001) and 18.3 % of the total variance in the left vST (R^2 = .164; $F_{(12,208)}$ = 3.867, p < .001). For the left vST, factor 2 (beta = 1.307, p = .022), diagnostic group (HC vs. BP: beta = -2.679, p = .006) and age (beta = -.087, p = .003) predicted activation. For the right vST, only diagnostic group (SZ vs. HC: beta = -4.137, p = .003; BP vs. HC: beta = -2.982, p = .005; ASD vs. HC: beta = -2.871, p = .008) and age (beta = - .095, p = .002) reached significance, whereas the dimensional factor showed a clear

trend (beta = 1.088, p = .077). None of the other above named regressors including all interaction terms reached significance (all p > .05).

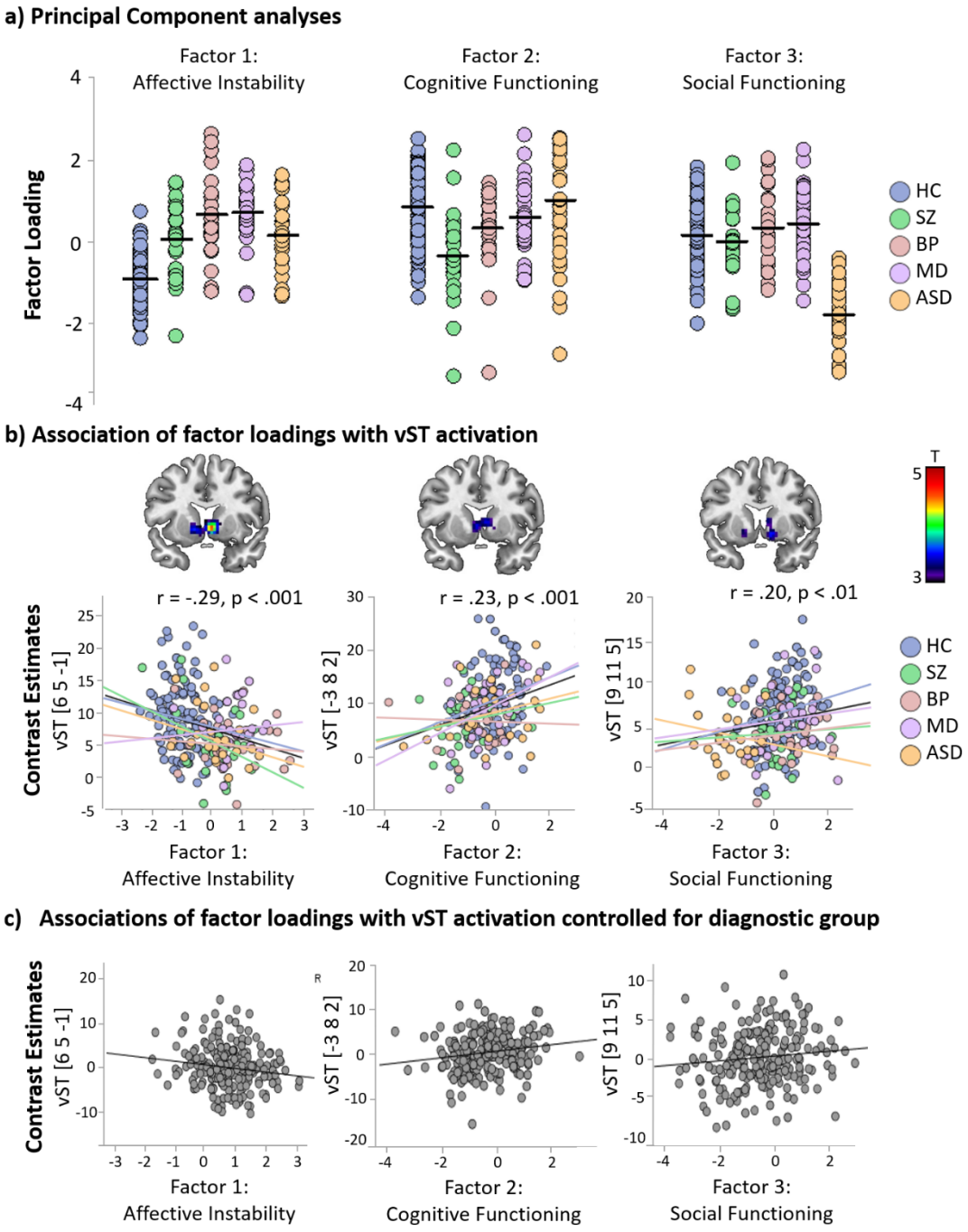

Figure 2.4: Dimensional Results. a) Group-specific factor loadings. b) Scatter plots depict associations between peak voxel contrast estimates in the ventral striatum (vST) and dimensional factors relating to affective instability (left), cognitive functioning (middle) and social functioning (right). Linear fit lines in black color refer to the full sample, while group-specific linear fit lines are depicted in color. c) Scatter plots display the partial correlation results between each factor and peak voxel contrast estimates in the vST while controlling for diagnostic group, age, sex and education. r: Pearson correlation coefficient, HC: healthy control, SZ: schizophrenia, BP: bipolar disorder, MD: major depression, ASD: autism spectrum disorder. For illustration, images were masked with the predefined vST mask and a significance threshold of p_{uncorr} < .005 was applied.

Table 2.3: Dimensional associations between transdiagnostic factor loadings and reward network activation as well as vST connectivity.

Region	k	x	y	z	*F/T*	p_{corr}
Activation						
FACTOR 1: - AFFECTIVE						
cerebellum L	40	-21	-76	-34	4.91	.009
lateral frontal gyrus R [Area 45]	51	57	20	17	4.91	.010
Superior medial frontal gyrus	15	3	35	35	4.87	.011
Superior medial frontal gyrus	12	3	29	53	4.52	.027
ventral striatum R*	49	6	5	-1	4.58	<.001
ventral striatum L*	13	-3	5	-1	3.44	.009
FACTOR 2: COGNITIVE						
ventral striatum L*	9	-3	8	2	3.15	.020
ventral striatum R*	8	6	8	5	3.11	.022
FACTOR 3: SOCIAL						
ventral striatum R*	1	9	11	5	2.81	.049
vST Connectivity						
FACTOR 1: - AFFECTIVE						
postcentral gyrus L [Area 4a]	74	-30	-31	68	5.78	<.001
inferior parietal lobule R [SPL(7A)]	60	27	-55	50	5.89	<.001
superior parietal cortex L [SPL (7A)]	26	-18	-64	62	5.50	.001
cuneus L	130	-6	-85	32	5.47	.002
insula L [Insula (Id1)]	18	-36	-16	-4	5.42	.002
superior temporal cortex R [TE 3]	12	66	-22	14	5.39	.002
putamen L	15	-27	-4	2	5.18	.006

Cluster extent *k* is given at $p_{corr} < .05$, family wise error (FWE) corrected for multiple comparisons within the whole brain for k > 10 voxels or within the *ventral striatum (vST) region of interest (ROI) using small volume correction (SVC). X-, y-, and z-coordinates (MNI) and statistical information refer to the peak voxel(s) in the corresponding cluster (voxel-level statistics). R: right, L: left.

Factor 3 (social functioning): Multiple regression analyses indicated that the above outlined predictors explained 14.7 % of the total variance in the right vST (R^2 = .147; $F_{(12,208)}$ = 2.988, p =

.001). Only diagnostic group (SZ vs. HC: beta = -2.117, p = .010; BP vs. HC: beta = -2.441, p = .003; and trend-wise ASD vs. HC: beta = -3.719, p = .057) and age (beta = -.051, p = .039) reached significance whereas the dimensional factor showed a clear trend (beta = .936, p = .070). None of the other above named regressors including all interaction terms reached significance (all p >.05).

Exploring condition-specific effects: In order to explore whether alterations in reward processing are rather driven by the neutral or reward component, we provide additional plots displaying categorical and dimensional results, assessed separately for the win and neutral condition using beta-values (Figure S2.2).

Control analyses and reliability study

Medication: Overall, most of the investigated peak voxel estimates were not associated with the total medication load and CPZ-e (all p > .05; see Table S2.6 for exceptions). In addition, peak voxel activation in the right vST did not differ between patients taking antipsychotics and patients not taking antipsychotics ($F_{(1,100)}$ = .065, p = .766).

Motion: Using partial correlation analyses, we demonstrated that second-level peak voxel estimates were not associated with mFD (all p > .05, see Table S2.6).

Monetary vs. Social Reward: Reward anticipation as defined by the differential response to win as compared to neutral cues (contrast win cue > neutral cue) led to a robust activation of the reward network, independent from reward type (Figure S2.3a). We did not differentiate between reward types in the main analyses given 1) previous evidence of overlapping neural substrates between monetary and social reward (Lin et al., 2012), which 2) was replicated in the present data. More precisely, monetary reward anticipation led to a significantly stronger activation of the reward network (monetary > social reward anticipation, (Figure S2.3b). The reverse contrast (social > monetary reward anticipation) yielded no significant effect. This quantitative (rather than qualitative) difference between reward types is illustrated in the overlap of brain activation (Figure S2.3c). Importantly, however, both reward types elicited activation in the reward network to a significant degree, including the ventral striatum (Figure S2.3c-d, Table S2.7). In addition, the analyses of the interaction (cue X task) revealed that group differences were not differentially impacted by reward type both for activation and functional connectivity analyses neither within the whole brain nor within our vST region of interest. This suggests that monetary and social reward is not processed differentially between diagnostic categories.

Effect of current depressive state: The main effect of group in vST activation was robust to differences in current depressive state (right vST: [12 8 -10], $F = 6.92$, $p_{FWE} < .002$, SVC; left vST: [- 12 5 -10], $F = 5.35$, $p_{FWE} < .020$, SVC). Similarly, the vast majority of categorical or dimensional effects persisted in identified peak voxels when accounting for current depressive state, and no association with depressive state was observed in most of these voxels (Table S2.8). A notable but expected exception is an association of current depressive state with peak voxel estimates in the striatum ($p \leq .41$) which previously reflected the effect of the affective factor (factor 1), given its strong conceptual overlap. Finally, within the MD group, mean activation in the vST was not related to current depressive state (left vST: $F = .566$, $p = .459$; right vST: $F = .048$, $p = .829$).

Exploring sex effects: We tested for sex effects and the interaction between diagnostic group and sex on vST activation. These analyses revealed no effect of sex on activation in the vST (main effect of sex: $F_{(4,211)} = 0.304$, $p = .582$; interaction effect group X sex: $F_{(4,211)} = 1.11$, $p = .351$; see Figure S2.4). However, since sex-specific subgroups are rather small, in particular for the MD ($N_{males} = 8$) and SZ group ($N_{females} = 9$), statistical power might be insufficient to detect sex effects, which calls for further studies with larger samples.

Reward Feedback: Independent of group, the presentation of win compared to neutral reward feedback activated an extended network including visual areas, the ACC and the anterior insula, as well as subcortical structures such as the thalamus, hippocampus and vST (see Table S2.9 and Figure S2.5a). Compared to HC, we observed higher vST activation during reward receipt in SZ and BP ($p_{FWE} < .05$, SVC), but not in MD and ASD (see Figure S2.5b and Table S2.9). However, while this activation cluster overlaps with our ROI in the vST, the main peak of the activation cluster is located within the bilateral putamen (see Figure S2.5b).

In order to investigate putative associations with dimensional factors, we again implemented the two-step approach as outlined above. In step 1 (one-sample t-test), factor 1 (affective instability) showed a positive association with bilateral vST activation, while factor 2 (cognitive functioning) showed a negative association with the left vST response during reward feedback (Table S2.9). No other associations were observed. The second analysis step (multiple regression analysis on the identified peak voxels) suggested that these associations were significantly impacted by categorical group differences since the effects turned insignificant as soon as diagnostic group was taken into account (left vST, factor 1: beta = .251, $p = .128$.; factor 2: beta = -.148, $p = .212$; right vST, factor 1: beta = .135, $p = .413$; Figure S2.5c). Although less pronounced than during reward anticipation, these effects are suggestive of transdiagnostic alterations during reward receipt with

opposite direction: Categorical differences were clearly driven by an *increased* response to reward feedback in SZ compared to HC, while the association with the dimensional factor reflecting affective instability was *positive*, and the association with the cognitive functioning factor was *negative*. These associations were, however, sufficiently explained by group differences and are thus difficult to interpret. In addition, interpretability of these findings is compromised by a suboptimal task design which does not allow to separate reward receipt from target presentation and subject response. Further studies with optimized task design are needed to follow up on this finding.

Test-Retest analyses: Test-retest analyses provided evidence for a fair-to-good reliability of reward-related brain activation (whole-brain: median ICC = 0.52, interquartile range (IQR) = [0.39 0.63]; vST mask: median ICC = 0.47, IQR = [0.39 0.56] (see Table S2.10 and Figure S2.6).

2.1.5 Discussion

This study aimed to confirm and extend current knowledge about alterations in reward anticipation in severe mental disorders by systematically examining the relation to disorder categories and functional dimensions. Our results show that alterations in vST-related networks constitute transdiagnostic phenotypes which 1) relate to affective, cognitive and social functioning across diagnoses and 2) are associated with alterations in frontal and parietal regions likely involved in executive control.

vST response alterations between and across nosological boundaries

We replicated the finding of reduced vST activation during reward anticipation in patients with SZ and demonstrated similar alterations in BP and ASD, lending further evidence to the cross-diagnostic relevance of this phenotype (Hägele et al., 2015). In contrast to some previous reports (Keren et al., 2018; Zhang et al., 2013), we did not find reduced vST responses in MD patients. Besides differences in medication and task design, this discrepancy might result from differences in current depressive state, which ranged from fully remitted to currently depressed in our MD sample. State-dependent vST alterations (Satterthwaite et al., 2015) might therefore be masked, although this was not supported by our control analyses. Interestingly, however, our dimensional approach nonetheless suggests an impact of affective functioning on reward processing, with higher affective instability (factor 1) relating to lower responses in the vST across diagnostic entities including MD. While this adds to recent transdiagnostic evidence (Arrondo et al., 2015; Hägele et al., 2015; Satterthwaite et al., 2015), we additionally show that this association is valid

for a broad definition of affective functioning based on a comprehensive collection of clinical measures representing diverse psychological constructs associated with a general risk for psychiatric disorders (Jeronimus, Kotov, Riese, & Ormel, 2016). These observations suggest that a dysfunctional regulation of affective symptoms relates to vST alterations across the psychiatric spectrum, likely reflecting blunted attribution of motivational salience to rewarding stimuli (Hägele et al., 2015).

We also observed an association with a dimensional measure of cognitive functioning (factor 2) where stronger vST responses related to better performance in neurocognitive tests. This suggests that cognitive deficits, such as deficits in working memory or cognitive flexibility, are relevant to reward anticipation in the context of incentive delay tasks which require a certain level of task comprehension and working memory capacity. Indeed, deficits in the ability to actively represent and maintain information about the task and the anticipated rewards have been suggested to contribute to blunted reward experience and anhedonia in SZ (Barch, 2005). Here we show that the relationship between striatal activation and cognitive functioning is not specific to SZ, but rather relates to the degree of cognitive impairment independent of diagnostic category.

Regarding social functioning (factor 3), higher scores related to higher vST responses, which was however not independent from diagnostic group. In fact, factor 3 was strongly driven by the ASD group. While a role of reward processing in ASD is well established (Clements et al., 2018), our dimensional analyses tentatively point to a transdiagnostic relationship between social functioning and vST response to reward anticipation.

In sum, our categorical approach suggests that vST functional alterations are present across several diagnostic categories. Moreover, our factor-analytical approach points to distinct brain-behavior relationships that exist across nosological boundaries. Supplemental analyses confirmed that the observed dimensional effects were not (factor 1 and 2) or only to a small extent (factor 3) explained by diagnostic category, emphasizing the higher sensitivity of our dimensional approach. This challenges more disorder-specific mechanistic theories of vST dysfunction (e.g., aberrant salience processing in SZ (Gradin et al., 2013); anhedonia in MD (Zhang et al., 2013); alterations in the behavioral activation system in BP (Urosević et al., 2008); social motivation deficits in ASD (Chevallier et al., 2012) and points to shared underlying neural mechanisms that could, for example, relate to the participation of the vST in separable processing loops (Haber & Knutson, 2010). As the limited spatial resolution prevents a more fine-grained structural characterization of the activation pattern associated with each factor, future studies should investigate whether the

localization of peak voxels might reflect the well-established pattern of a dorsal-cognitive to ventral-affective gradient in the striatum (Haber & Knutson, 2010). Similarly, our supplemental finding of potential transdiagnostic alterations in the vST during reward receipt should be followed up using optimized task designs, for example jittered target-receipt intervals and a higher number of trials allowing for the comparison of successful and non-successful win trials.

Neural networks linked to reward processing

Beyond the vST, we adopted a brain-wide perspective to explore the distributed networks relevant for dimensional or categorical effects of reward processing which converged on regions related to the fronto-parietal network (FPN), specifically on the IPL and prefrontal areas: Categorical whole-brain analyses revealed reduced brain responses in these regions, most prominently in BP for activation, and in SZ and BP for vST connectivity. Dimensional analyses suggest higher affective instability (factor 1) to relate to lower responses in lateral prefrontal regions, as well as to reduced vST connectivity with the IPL.

Our observation of altered functional responses in regions involved in executive control, in particular in BP and SZ patients, aligns with previous findings (Anand, Li, Wang, Lowe, & Dzemidzic, 2009; Diwadkar et al., 2014; Dutra, Man, Kober, Cunningham, & Gruber, 2017; Meyer-Lindenberg et al., 2002; Ongür et al., 2010; Orliac et al., 2013; Sarpal et al., 2015; Urošević, Luciana, Jensen, Youngstrom, & Thomas, 2016). In line with our results, a recent study showed that higher genetic risk for psychotic disorders was associated with aberrant integration of information across networks for attention (including the FPN) and the striatum (Diwadkar et al., 2014), suggesting a disrupted crosstalk between the executive control and reward network. Our dimensional approach additionally suggests that alterations in executive control areas constitute a shared phenotype across nosological boundaries and relate to affective regulation deficits.

The importance of a tight interaction between the executive control and reward networks is well described (Braver et al., 2014; Pessoa, 2015). Reward cues facilitate the allocation of processing resources towards behaviorally important stimuli (Redgrave & Gurney, 2006), which is reflected by increased FPN activation (Gilbert & Fiez, 2004; Mohanty, Gitelman, Small, & Mesulam, 2008; Small et al., 2005) and connectivity with the reward network (Camara, Rodriguez-Fornells, Ye, & Münte, 2009). The observed association of control network function with affective instability might reflect reduced processing capacities across psychiatric conditions as a result of affective symptom load. This interpretation follows a recent, transdiagnostic theory of psychiatric

dysfunction (Cole et al., 2014) which postulates that the experience and regulation of symptoms such as depressed mood or paranoid ideation consumes cognitive resources and results in limited flexibility of large-scale control networks.

Strengths and limitations

This study faced several challenges common to clinical imaging (Greene et al., 2016). We controlled for basic demographic variables and showed that neither CPZ-e nor total medication were related to striatal responses. We carefully balanced our sample for several quality parameters, showed that results were not related to motion, and demonstrated fair-to-good reliability of task effects in an independent test-retest sample. Our PCA approach comes with the limitation that resulting components depended on the specific test battery, which we addressed by a broad coverage of domains and assessments. Conversely, this approach offers several advantages for dimensional analyses: 1) The resulting components are maximally independent, 2) do not rely on single, often disorder-specific clinical measures with low variance in healthy subjects, 3) do not focus on single psychopathological processes not considering other psychological variables, and 4) reduce the selection bias of single measures out of a large questionnaire and test battery that is usually acquired in clinical studies (Greene et al., 2016).

Despite these efforts, we acknowledge that we cannot rule out the possibility of unaddressed influences of some confounders, in particular potential interaction effects of medication. This issue needs to be addressed in larger-scale studies that allow for the comparison of medicated and unmedicated patients, favorably within and across diagnostic groups. In addition, the inclusion of other diagnostic groups known to show alterations in reward processing (e.g., obsessive-compulsive disorder), the systematic consideration of current disease state (e.g., current episode vs. remission states in MD) and comorbidities (e.g., type, number, lifetime vs. concurrent), and a better matching of groups on demographic characteristics (e.g., sex, age and education) would have been desirable but were beyond the feasible scope of the present study. Finally, we did not correct for the number of tests resulting from this complex research question in order to maximize sensitivity. Also, we acknowledge that our results might to some degree be influenced by the choice of analytical methods, such as preprocessing strategies, statistical models, and the choice of significance assessment (e.g., voxel-level vs. cluster-level significance).

However, while methodologically very challenging, our approach of jointly investigating different patient groups in the same study comes with the valuable advantage of ruling out methodological differences when comparing results between different diagnoses. Prospectively, there will be a need to conduct large-scale, pre-registered, multi-site and multi-diagnosis research to overcome the heterogeneity of findings generated by smaller-sized studies.

2.1.6 Conclusion

The present study demonstrates reward processing alterations in a range of psychiatric disorders. Using dimensional, behaviorally meaningful measures covering affective, cognitive and social functioning, we further demonstrate that independent psychological domains relate to altered vST activation across the psychiatric spectrum, thereby informing current disorder-specific mechanistic theories of vST dysfunction. Beyond the vST, our results tentatively point to transdiagnostic alterations in the interaction between the reward and executive control network, suggesting that the symptom-induced reduction of cognitive control capacities might constitute a superordinate transdiagnostic factor mediating domain specific differences such as blunted striatal functioning. Our results can inform the development of therapeutic interventions targeting specifically the enhancement of cognitive control abilities in mental disorders (e.g., attentional training techniques included in the metacognitive therapy (Wells & Simons, 2013) and provide a biological account of the underlying pathophysiological landscape of mental illness that can inform both categorical and domain-related accounts of psychiatric nosology. Furthermore, our data indicate good reliability and robustness against common clinical confounders, indicating that similar measures may usefully contribute to biomarkers in the clinic and thus be useful in precision medicine approaches in psychiatry.

2.1.7 Supplemental Information

TABLES

Table S2.1: Medication and comorbidities.

Group	SZ	BP	MD	ASD	Sum
CPZ-e	415.0 (45.2)	123.8 (42.7)	16.7 (41.3)	3.3 (47.1)	129.9 (271.1)
medication load	2.8 (0.3)	2.6 (0.3)	1.7 (0.3)	0.4 (0.3)	1.9 (1.8)
tricyclic antidepressants	2	0	2	0	4
SSRI	7	7	15	3	32
other antidepressants	1	2	8	1	12
typical antipsychotics	4	1	0	1	6
atypical antipsychotics	24	18	6	1	49
lithium	0	10	2	1	13
other mood stabilizers	5	19	5	1	30
anticonvulsants	4	12	2	0	18
methylphenidate	0	0	0	2	2
comorbidities					
alcohol abuse	2	2	1	1	6
cannabis abuse	5	3	1	0	9
depression	2	0	-	12	14
anxiety	0	0	2	3	5
other	1	3	2	2	8

Displayed are mean values (standard error) and number of cases (comorbidities); HC: healthy control, SZ: schizophrenia, BP: bipolar disorder, MD, major depression, ASD: autism spectrum disorder, CPZ-e: chlorpromazine equivalents, medication load as described in Hassel and colleagues (2008), SSRI: selective serotonin reuptake inhibitor.

Table S2.2: Group differences in quality parameters before and after adjusting the sample for motion outliers.

	INITIAL SAMPLE: BEFORE QUALITY ASSURANCE PROCEDURES						**FINAL SAMPLE: AFTER QUALITY ASSURANCE PROCEDURES**					
Group	**HC**	**SZ**	**BP**	**MD**	**ASD**	**Between-group differences**	**HC**	**SZ**	**BP**	**MD**	**ASD**	**Between-group differences**
N	129	42	38	38	32		110	27	28	31	25	
Movement: Power's FD	0.20 (0.01)	0.32 (0.02)	0.29 (0.02)	0.25 (0.02)	0.24 (0.02)	$F_{(4,289)} = 7.76$, $p < .001$	0.18 (0.06)	0.20 (0.01)	0.20 (0.01)	0.20 (0.01)	0.18 (0.1)	$F_{(4,216)} = 1.56$, $p = .185$
Movement: total translation (mm)	0.74 (0.1)	1.32 (0.1)	1.08 (0.1)	0.84 (0.1)	1.17 (0.1)	$F_{(4,289)} = 5.47$, $p < .001$	0.69 (0.04)	0.71 (0.08)	0.76 (0.08)	0.75 (0.07)	0.86 (0.08)	$F_{(4,216)} = 0.91$, $p = .461$
Movement: total rotation (degrees)	0.65 (0.1)	1.08 (0.1)	1.00 (0.1)	0.71 (0.1)	1.00 (0.1)	$F_{(4,289)} = 2.94$, $p = .021$	0.62 (0.04)	0.48 (0.09)	0.63 (0.08)	0.69 (0.08)	0.78 (0.09)	$F_{(4,216)} = 1.62$, $p = .171$
Signal-to-Noise-Ratio	86.98 (1.3)	80.55 (2.3)	87.56 (2.4)	88.33 (2.4)	83.35 (2.6)	$F_{(4,289)} = 2.174$, $p = .072$	87.67 (1.4)	83.63 (2.9)	84.62 (2.8)	89.22 (2.7)	85.9 (3.0)	$F_{(4,216)} = 0.78$, $p = .537$
Signal-to-Fluctuation-Noise-Ratio	310.86 (7.9)	270.99 (13.8)	271.16 (14.5)	316.93 (14.5)	299.94 (15.8)	$F_{(4,289)} = 2.90$, $p = .022$	316.00 (7.9)	309.68 (16.3)	302.65 (15.7)	329.00 (14.9)	332.64 (16.6)	$F_{(4,216)} = 0.64$, $p = .632$
Signal-to-Ghost-Ratio	20.16 (0.2)	19.43 (0.4)	19.89 (0.5)	19.80 (0.5)	19.58 (0.5)	$F_{(4,289)} = 0.72$, $p = .582$	20.27 (0.3)	19.25 (0.5)	19.99 (0.5)	19.91 (0.5)	19.77 (0.5)	$F_{(4,216)} = 0.83$, $p = .507$

Displayed are mean values (standard error); HC: healthy control; SZ: schizophrenia; BP: bipolar disorder, MD: major depression; ASD: autism spectrum disorder; FD: frame-wise displacement (Power et al., 2012).

Table S2.3: (Neuro)psychological measures and respective factor loadings and communalities.

	Measures	Abbr.	Factor 1: affective	Factor 2: cognitive	Factor 3: social	Com.
1	Verbal learning and memory test - Version A (sum of correct words in 5 learning trials) (Helmstaedter, Lendt, & Lux, 2001)	VLMT	-.091	**.691**	.116	.499
2	Trail Making Tests A, B (reaction time) (Reitan, 1979; Tombaugh, 2004)	TMT-A TMT-B	.141 .044	**-.657** **-.727**	-.001 -.111	.452 .543
3	Digit Span (sum score) (Tewes, 1991; Wechsler, 1955)	ds	-.080	**.640**	-.095	.425
4	D2 concentration test - total number (Brickenkamp, Schmidt-Atzert, & Liepmann, 2010)	D2	-.126	**.661**	-.016	.453
5	Word fluency (Aschenbrenner, Tucha, & Lange, 2001): letter animal	 wf letter wf animal	 -.107 -.111	 **.670** **.690**	 .090 .039	 .469 .489
6	Digit-symbol test (Tewes, 1991; Wechsler, 1955)	ds	-.148	**.750**	.065	.588
7	Matrices test (Tewes, 1991; Wechsler, 1955)	Matrices	.065	**.597**	.049	.363
8	Multiple-choice vocabulary intelligence test (Mehrfachwahl-Wortschatz-Test-B) (Lehrl, 2005)	MWTB	-.004	**.605**	.103	.377
9	Reading the Mind in the eyes test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001)	RTME	.126	.311	.390	.265
10	Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Hautzinger et al., 1995)	BDI	**.778**	-.208	.049	.652
11	State-Trait Anxiety Inventory (Laux, Glanzmann, Schaffner, & Spielberger, 1981): State Trait	 STAI-S STAI-T	 **.727** **.895**	 -.163 -.115	 -.086 -.057	 .562 .817
12	Autism Quotient (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001; Freitag et al., 2007)	AQ	**.509**	-.058	**-.647**	.682
13	Adult ADHD self-report scale (R.C. Kessler et al., 2005)	ASRS	**.778**	-.094	-.085	.621
14	Buss-Perry Aggression Questionnaire (Buss & Perry, 1992)	BPAQ	**.576**	-.029	-.318	.434
15	Emotion Regulation Questionnaire (Abler & Kessler, 2009): Reappraisal Suppression	 ERQ-R ERQ-S	 **-.448** .352	 .034 .191	 **.453** -.230	 .407 .213

	Measures	Abbr.	Factor 1: affective	Factor 2: cognitive	Factor 3: social	Com.
16	Barrat Impulsiveness Scale version 11 (Patton, Stanford, & Barratt, 1995)	BIS	**.676**	-.182	.053	.493
17	Schizotypal Personality Questionnaire (Raine, 1991)	SPQ	**.763**	-.166	-.298	.699
18	NEO Five factor inventory (Borkenau, P. & Ostendorf, 2008):					
	Extraversion	NEO-E	**-.642**	-.052	**.447**	.615
	Conscientiousness	NEO-C	**-.696**	-.034	-.114	.499
	Neuroticism	NEO-N	**.873**	-.101	-.107	.784
	Openness	NEO-O	-.004	.283	**.526**	.356
	Agreeableness	NEO-A	-.304	.008	**.729**	.623
19	Interpersonal Reactivity Index (Davis, 1980)	IRI	.130	.002	**.835**	.714
20	Toronto Alexithymia Scale (Bagby, Parker, & Taylor, 1994; Popp et al., 2007)	TAS	**.665**	-.043	**-.469**	.664
21	Action Control Scale (Kuhl, 1994):					
	Action orientation subsequent to failure	HAKEMPA OF AOD AOP	**-.750**	.051	.078	.571
	Prospective and decision-related action orientation		**-.764**	.054	-.033	.587
	Action orientation during (successful) performance		-.293	.202	.061	.130
22	Brief Self Control Scale (Bertrams & Dickhäuser, 2009; Tangney, Baumeister, & Boone, 2004)	BSCS	**-.788**	.018	-.021	.622

Measures 1 to 9 were collected in a neuropsychological test session; questionnaires (10 – 22) were filled out in an online test session. Values in bold represent factor loadings > .4. Com.: communalities, Abbr.: Abbreviation.

Table S2.4: Post-hoc group differences in vST brain responses.

Region	k	x	y	z	T	p_{corr}
HC > SZ						
ventral striatum R	36	12	8	-10	3.56	.008
HC > BP						
ventral striatum R	70	6	8	-4	4.35	<.001
ventral striatum L	68	-9	8	-10	3.78	.004
HC > ASD						
ventral striatum R	45	12	8	-10	3.51	.009
ventral striatum L	16	-12	8	-7	3.00	.039
MD > BP						
ventral striatum R	32	12	20	-4	3.72	.005

Cluster extent *k* is given at P_{corr} < .05, family wise error corrected for multiple comparisons within the ventral striatum (vST) region of interest for k > 10 voxels. X-, y-, and z-coordinates (MNI) and statistical information refer to the peak voxel(s) in the corresponding cluster. Note that only contrasts with significant activation effects are displayed. HC: healthy controls, SZ: schizophrenia, BP: bipolar disorder, MD: major depressive disorder, ASD: autism spectrum disorder; R: right, L: left.

Table S2.5: Post-hoc group differences in whole brain results.

Region	k	x	y	z	T	p_{corr}
Activation						
HC > BP						
postcentral gyrus L	151	-30	-25	38	6.16	<.001
superior occipital gyrus R [IPC (PGp)]	294	33	-70	41	5.70	<.001
inferior parietal cortex L [IPC (PFm)]	353	-39	-61	50	5.61	<.001
supplementary motor area R	99	12	23	47	5.53	.001
middle frontal gyrus R	85	39	53	-4	5.52	.001
inferior frontal gyrus R [Area 45]	147	51	35	23	5.42	.001
precentral gyrus R	65	30	-13	38	5.26	.002
precuneus L [SPL (7P)]	60	-6	-76	47	5.25	.002
precentral gyrus L	28	-30	8	38	5.08	.005
inferior temporal gyrus L	38	-39	-40	-10	5.04	.006
middle cingulate gyrus R	57	9	-34	32	5.03	.006
inferior frontal gyrus L	20	-39	44	-10	4.76	.018
vST - Connectivity						
HC > SZ						
superior parietal cortex R [hIP3]	47	33	-61	53	5.92	<.001
cerebelllum R [Lobule VI (Hem)]	50	33	-43	-40	5.75	<.001
postcentral gyrus L [Area 2]	32	-42	-43	59	5.54	.001
cerebelllum R [Lobule VIIa Crus I (Hem)]	14	36	-67	-43	5.13	.007
HC > BP						
fusiform gyrus L	91	-24	-70	-16	5.68	.001
superior occipital gyrus L	70	-15	-88	20	5.44	.002
superior parietal cortex R [SPL (7A)]	17	27	-58	50	5.16	.006
cuneus R [Area 18]	35	6	-88	17	5.06	.009
lingual gyrus R [Area 17]	15	24	-70	-1	4.92	.016

Cluster extent *k* is given at $p_{corr} < .05$, family wise error corrected for multiple comparisons across the whole brain for k > 20 voxels. X-, y-, and z-coordinates (MNI) and statistical information refer to the peak voxel(s) in the corresponding cluster. Regions were classified according to the Automated Anatomical Labeling Atlas (Tzourio-Mazoyer et al., 2002). If applicable, functional labels were added in square brackets based on Anatomical Probability Maps (Anatomy toolbox (Eickhoff, Heim, Zilles, & Amunts, 2006)). Note that only contrasts with significant effects are displayed. HC: healthy controls, SZ: schizophrenia, BP: bipolar disorder, MD: major depressive disorder, ASD: autism spectrum disorder; R: right, L: left.

Table S2.6: Control analyses on medication and motion.

Analysis approach	Region	medication load		CPZ-e		mFD	
		r	*p*	*r*	*p*	*r*	*p*
Categorical analyses	**Activation**						
	ventral striatum R	-.015	.880	-.038	.694	.063	.352
	ventral striatum L	-.030	.759	.000	.996	.059	.385
	inferior parietal lobule L	**-.197**	**.041**	**.265**	**.006**	-.066	.332
	inferior parietal lobule R	-.026	**.** 792	-.102	.295	-.003	.963
	inferior frontal gyrus R	.038	.698	.128	.187	-.074	.280
	vST Connectivity						
	inferior parietal lobule R	-.172	.075	-.034	.726	-.112	.100
	fusiform L	-.069	.480	.147	.129	-.068	.321
	cerebellum R	-.131	.176	-.050	.611	.137	.102
Dimensional analyses	**Activation**						
	FACTOR 1: - AFFECTIVE						
	ventral striatum R	.009	.926	.054	.578	.067	.328
	ventral striatum L	-.084	.387	.004	.969	.036	.594
	cerebellum R	-.123	.203	.049	.611	-.081	.235
	inferior frontal gyrus R	.037	.702	.146	.131	-.034	.614
	superior medial frontal gyrus	.095	.329	.185	.056	-.019	.784
	FACTOR 2: COGNITIVE						
	ventral striatum L	-.099	.310	-.012	.901	.049	.475
	ventral striatum R	-.010	.914	.089	.359	.066	.335
	FACTOR 3: SOCIAL						
	ventral striatum R	-.009	.923	-.129	.185	.064	.344
	vST Connectivity						
	FACTOR 1: - AFFECTIVE						
	inferior parietal lobule R	-.071	.468	.030	.756	-.118	.081
	superior parietal cortex L	-.152	.116	-.058	.553	.004	.955
	cuneus L	**-.242**	**.012**	-.055	.573	-.124	.067
	insula L	**.202**	**.036**	**.223**	**.020**	.077	.260
	superior temporal cortex R	-.001	.990	.034	.726	-.069	.307
	putamen L	-.068	.482	.183	.057	.065	.339

Partial correlation between peak voxel estimates and total medication load/chlorpromazine dose equivalents (CPZ-e) (N = 106) and mean frame-wise displacement (mFD) (Power et al., 2012) (N = 221) controlling for age, sex and education. Regions were classified according to the Automated Anatomical Labeling Atlas (Tzourio-Mazoyer et al., 2002). r: Pearson correlation coefficient, R: right, L: left. Significant associations are bold.

Table S2.7: Effect of reward anticipation (win cue > neutral cue) and modulation by reward type (monetary, social) in the vST.

Region	k	x	y	z	*F*	p_{corr}
Cue win > cue neutral						
ventral striatum R	62	9	8	-1	431.36	<.001
ventral striatum L	63	-9	5	2	375.71	<.001
Social cue win > cue neutral						
ventral striatum R	62	9	8	-1	226.43	<.001
ventral striatum L	63	-9	5	2	183.25	<.001
Monetary cue win > cue neutral						
ventral striatum R	62	9	8	-4	380.66	<.001
ventral striatum L	63	-9	5	2	328.05	<.001
Interaction cue X task						
ventral striatum R	60	9	8	-4	83.02	<.001
ventral striatum L	30	-12	11	-1	61.26	<.001

Cluster extent *k* is given at P_{corr} < .05, family wise error corrected for multiple comparisons within the ventral striatum (vST) mask for k > 10 voxels. X-, y-, and z-coordinates (MNI) and statistical information refer to the peak voxel(s) in the corresponding cluster. R: right, L: left.

Table S2.8: Control analyses of group effect and current depressive state.

Analysis approach	Region	effect of group or dimensional factor		effect of depressive state	
		F	*p*	*F*	*p*
Categorical analyses	**Activation**				
	ventral striatum R	**6.520**	**.000**	.192	.662
	ventral striatum L	**4.503**	**.002**	.034	.854
	inferior parietal lobule L	**6.778**	**.000**	.044	.834
	inferior parietal lobule R	**5.659**	**.000**	.673	.413
	inferior frontal gyrus R	**4.526**	**.002**	1.832	.177
	vST Connectivity				
	inferior parietal lobule R	**8.755**	**.000**	.187	.666
	fusiform L	**8.301**	**.000**	.000	.987
	cerebellum R	**8.920**	**.000**	2.095	.149

Analysis approach	Region	effect of group or dimensional factor		effect of depressive state	
		F	*p*	*F*	*p*
Dimensional analyses	**Activation**				
	FACTOR 1: - AFFECTIVE				
	ventral striatum R	1.688	.154	**4.235**	**.041**
	ventral striatum L	2.060	.087	**6.234**	**.013**
	cerebellum R	**2.873**	**.024**	**5.432**	**.021**
	inferior frontal gyrus R	**2.634**	**.035**	2.209	.139
	superior medial frontal gyrus	**3.291**	**.012**	1.739	.189
	superior medial frontal gyrus	**2.725**	**.030**	.048	.826
	FACTOR 2: COGNITIVE				
	ventral striatum L	**2.499**	**.044**	.000	.995
	ventral striatum R	**3.870**	**.005**	1.207	.273
	FACTOR 3: SOCIAL				
	ventral striatum R	**4.073**	**.003**	.656	.419
	vST Connectivity				
	FACTOR 1: - AFFECTIVE				
	postcentral gyrus L	2.044	.089	1.775	.184
	inferior parietal lobule R	**5.019**	**.001**	.743	.390
	superior parietal cortex	**3.433**	**.010**	2.814	.095
	cuneus L	**5.498**	**.000**	.689	.407
	insula L	**3.023**	**.019**	1.233	.268
	superior temporal cortex R	1.782	.134	3.070	.081
	putamen L	**2.533**	**.041**	.286	.593

Effect of group and effect of current depressive state at identified peak voxel estimates while controlling for diagnosis, sex, age, education, and mean frame-wise displacement (Power et al., 2012). Regions were classified according to the Automated Anatomical Labeling Atlas (Tzourio-Mazoyer et al., 2002). Current depressive state (not depressed, mildly depressed, moderately depressed, severely depressed) was assessed using the Beck Depression Inventory (BDI) (Hautzinger et al., 1995). R: right, L: left. Significant effects are displayed in bold.

Table S2.9: Reward feedback results.

Region	k	x	y	z	T/F	p_{corr}
fb win > fb neutral						
inferior occipital gyrus R	17995	33	-94	-7	25.33	<.001
inferior occipital gyrus L		-27	-94	-7	23.18	<.001
anterior cingulate gyrus R		3	41	8	15.74	<.001
anterior insula R		33	20	-16	14.16	<.001
anterior insula L		-33	14	-16	13.50	<.001
hippocampus L		-15	-7	-19	11.96	<.001
parahippocampal gyrus R		15	-7	-19	11.15	<.001
inferior parietal gyrus R	41	54	-40	56	5.96	<.001
precentral gyrus	39	-48	-1	56	5.73	<.001
superior frontal gyrus R	35	33	-7	71	5.59	<.001
ventral striatum R*	-	6	2	2	10.26	<.001
ventral striatum L*	-	-3	5	-1	9.45	<.001
Categorical results: ME of group						
Putamen R	61	21	8	-10	11.21	.001
Putamen L	9	-21	5	-10	8.99	.007
ventral striatum R*	-	15	14	5	5.61	.009
ventral striatum L*	-	-15	17	5	5.60	.009
Dimensional results						
Factor 1 - affective						
ventral striatum R*	-	12	11	-10	3.19	.031
ventral striatum L*	-	-9	8	13	3.95	.003
Factor 2 - cognitive						
ventral striatum L*	-	-9	8	13	3.28	.024

Cluster extent *k* is given at $p_{corr} < .05$, family wise error corrected for multiple comparisons within the whole brain or *ventral striatum (vST) region of interest. X-, y-, and z-coordinates (MNI) and statistical information refer to the peak voxel(s) in the corresponding cluster. R: right, L: left, fb: feedback, ME: main effect, HC: healthy controls, SZ: schizophrenia, BP: bipolar disorder, MD: major depressive disorder, ASD: autism spectrum disorder.

Table S2.10: Test-Retest Reliability.

	Percent ICC >.4	Median ICC (IQR)
Whole brain	.74	.52 (.39 .63)
ROI vST	.72	.47 (.39 .56)

ICC: intraclass correlation coefficient, IQR: interquartile range (Q1 Q3), ROI: region of interest, vST: ventral striatum

FIGURES

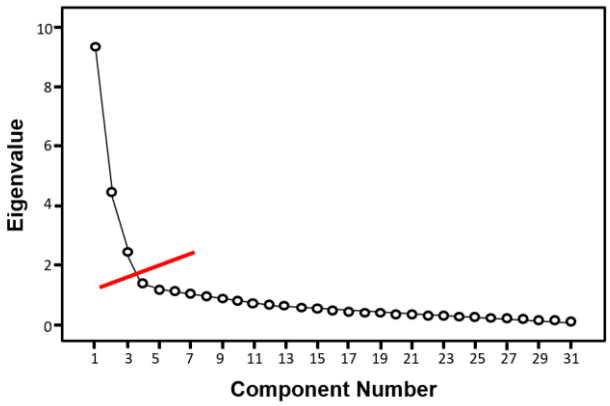

Figure S2.1: Scree Plot analysis.

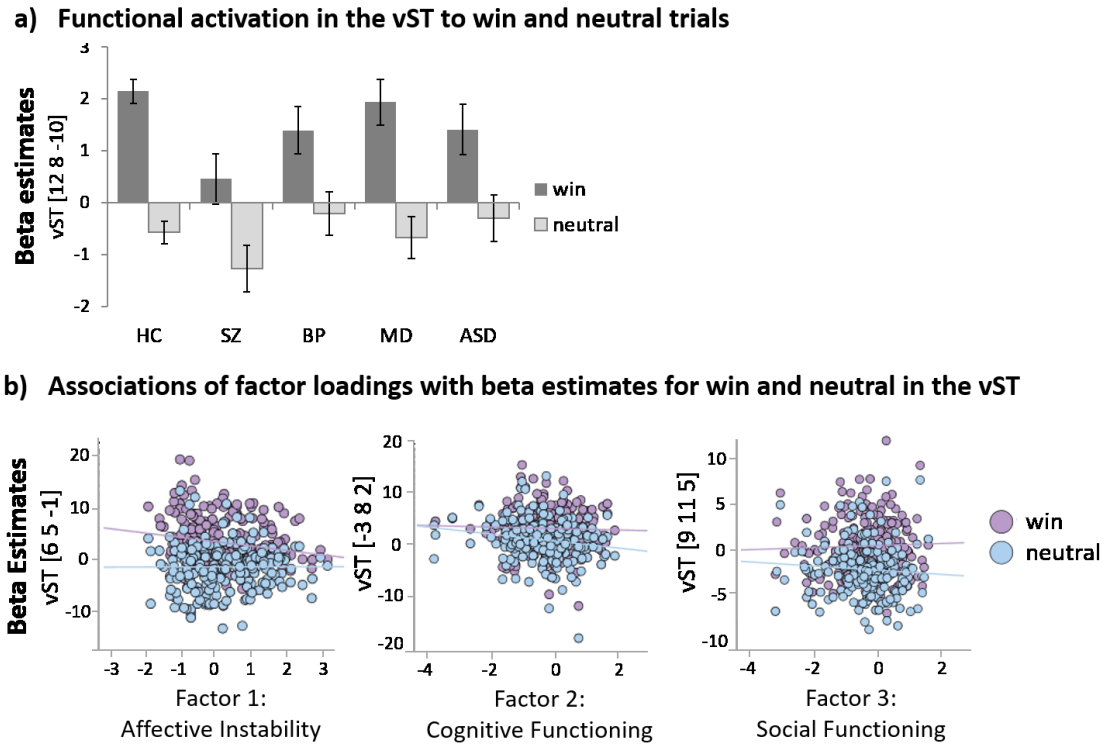

Figure S2.2: vST response in win vs. neutral trials. a) Bar graphs depict beta-values for the win and neutral condition, extracted from the peak voxel of the main effect of group in the ventral striatum (vST). b) Scatter plots depict associations between factor loadings and beta-estimates for win and neutral conditions, extracted from the same voxels as in Figure 2.4, panels B-C. HC: healthy control, SZ: schizophrenia, BP: bipolar disorder, MD: major depression, ASD: autism spectrum disorder.

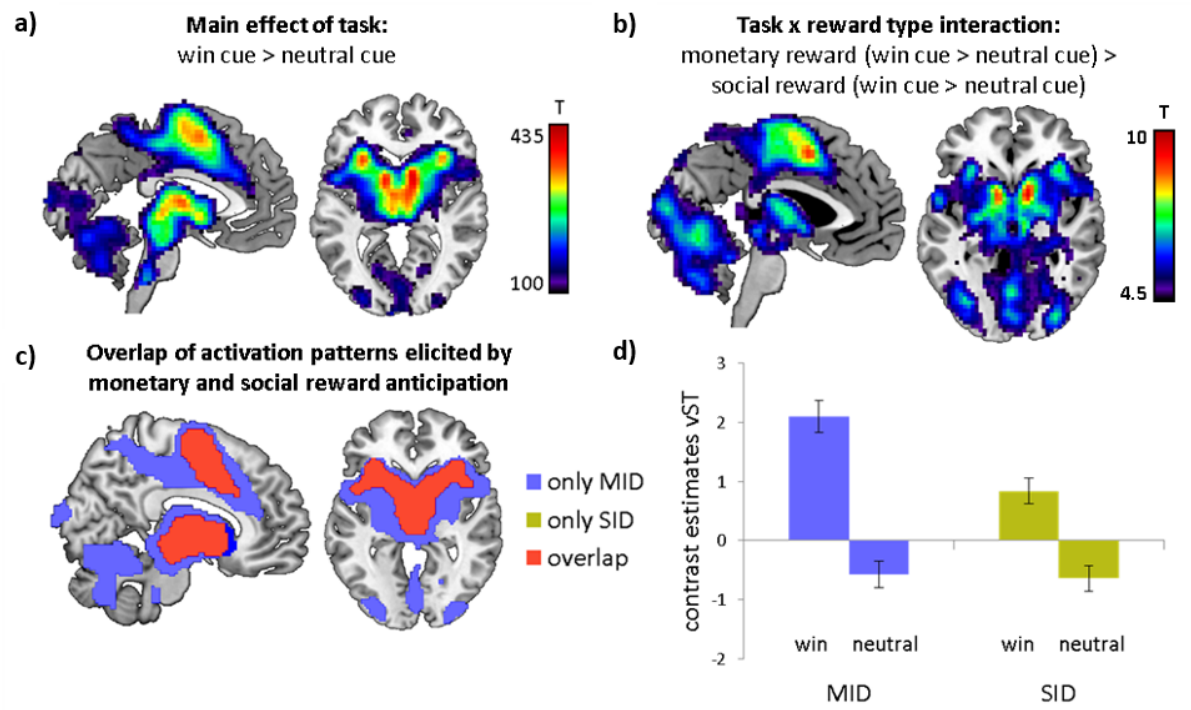

Figure S2.3: Whole-brain activation in response to reward anticipation (main effect of task) and modulation by reward type (monetary, social). a) Whole brain activation in response to reward anticipation (main effect of task); b) Effect of reward type on whole brain activation in response to reward anticipation (directed interaction effect); c) overlap of whole brain effects of social and monetary reward anticipation, defined at a threshold of F = 80; d) Plotted contrast estimates (mean, SE) of the ventral striatum (vST) in the win and neutral condition for both reward types.

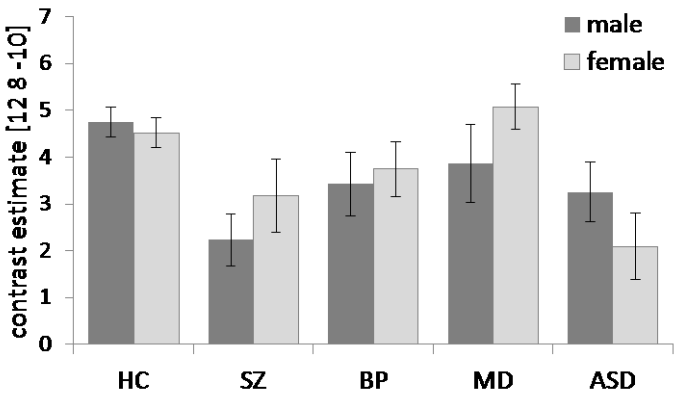

Figure S2.4: Sex-specific vST responses. Plotted contrast estimates (mean, SE) of ventral striatum (vST) responses to reward anticipation (cue win > cue neutral), plotted separately for males and females in each diagnostic group. HC: healthy control, SZ: schizophrenia, BP: bipolar disorder, MD: major depressive disorder, ASD: autism spectrum disorder.

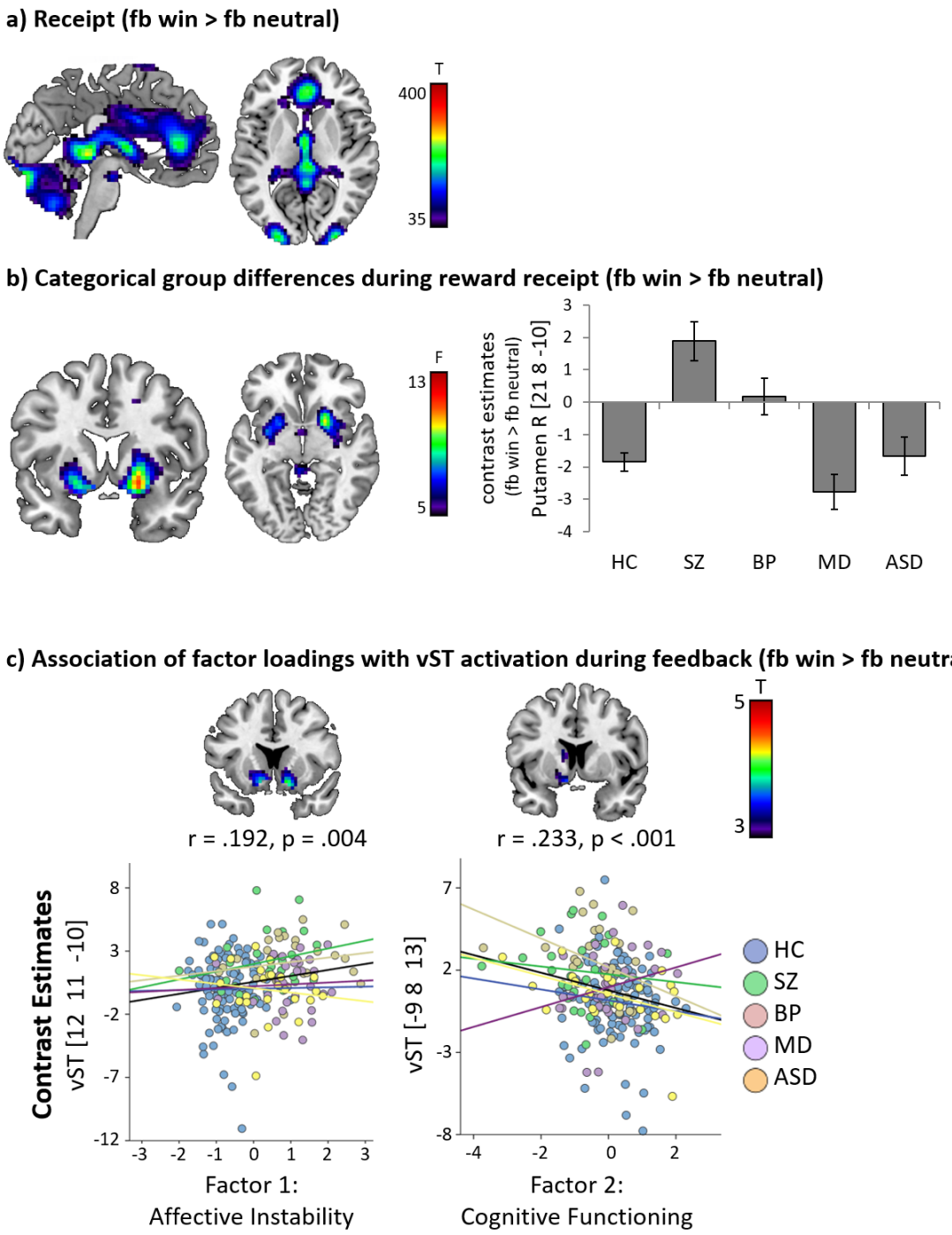

Figure S2.5: Reward feedback results. a) Main effect of task for reward feedback (feedback (fb) win > fb neutral). b) Categorical group differences in brain responses during reward feedback and plotted contrast estimates (mean, SE) of the right putamen. c) Scatter plots depict associations between peak voxel contrast estimates in the ventral striatum (vST) and dimensional factors relating to affective instability (factor 1, left) and cognitive functioning (factor 2, right). Linear fit lines in black color refer to the full sample, while group-specific linear fit lines are depicted in group-specific colors. HC: healthy control, SZ: schizophrenia, BP: bipolar disorder, MD: major depression, ASD: autism spectrum disorder. For illustration, a significance threshold of $p_{uncorr} < .001$ (panel a and b) or $p_{uncorr} < .005$ (panel c) was applied.

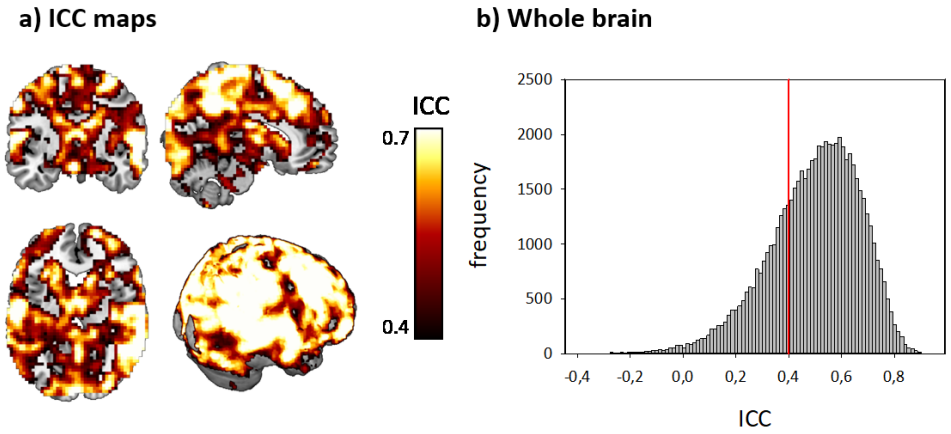

Figure S2.6: Test-retest reliability results. a) ICC (3,1)-maps (i.e., single-voxel reliability). b) Graph depicting frequency plot across the whole brain. The red vertical line indicates the threshold of ICC > 0.4, denoting fair or better reliability. ICC: intra-class correlation coefficients.

2.2 Study 2 – Ventral striatal-hippocampus coupling during reward processing as a (stratification) biomarker for psychotic disorders[2]

2.2.1 Abstract

Background: Altered vST activation to reward expectancy is a well-established intermediate phenotype for psychiatric disorders, specifically schizophrenia. Preclinical research suggests that striatal alterations are related to a reduced inhibition by the hippocampal formation. This circuit was recently highlighted as a novel drug-candidate for psychosis. However, its clinical relevance in humans has not been shown yet.

Methods: We performed functional magnetic resonance imaging during reward processing in 730 individuals including healthy controls (N = 397), patients (schizophrenia: N = 45; bipolar disorder: N = 45; major depressive disorder: N = 60), and unaffected first-degree relatives (schizophrenia: N = 46; bipolar disorder: N = 51; major depressive disorder: N = 86). We assessed disorder-specific differences in functional vST-hippocampus coupling as well as transdiagnostic associations with clinically relevant measures of positive, negative, and cognitive symptoms. We also probed the genetic underpinnings using polygenic risk scores for schizophrenia in a subset of healthy participants (N = 295).

Results: Functional vST-hippocampus coupling was 1) reduced in patients with schizophrenia, bipolar disorder, and first-degree relatives of patients with schizophrenia (p_{FWE} <.05, small-volume corrected), 2) linked to genetic risk for SZ (p = .035) and 3) associated transdiagnostically to dimensional measures of positive (r = -.14, p < .001) and cognitive (r = .13, p = .001), but not negative symptoms (p > .05).

Conclusion: We provide evidence that reduced vST-hippocampus coupling during reward processing is an endophenotype for schizophrenia linked to positive and cognitive symptoms, supporting current preclinical models of the emergence of psychosis. Moreover, our data indicate that vST-hippocampus coupling is familial and linked to polygenic scores for schizophrenia, supporting the use of this measure as an intermediate phenotype for psychotic disorders.

[2] **In Review**: Schwarz K., Moessnang C., Schweiger J.I., Harneit A.; Schneider M., Chen J., Cao H., Schwarz E., Witt S.H., Rietschel M., Nöthen M., Degenhardt F., Wackerhagen C., Erk S., Walter H., Tost H., Meyer-Lindenberg A. (in review). Ventral striatal-hippocampus coupling during reward processing as a (stratification) biomarker for psychotic disorders. *Biological Psychiatry*.

2.2.2 Introduction

Reduced vST activation during reward anticipation is a well-established phenotype in patients with SZ (Radua et al., 2015). Blunted vST activation has been detected in unaffected first-degree relatives with SZ (Grimm et al., 2014) and linked to polygenic risk (PGR) scores for psychotic disorders (Lancaster et al., 2016), suggesting a genetic underpinning of this phenotype. While a growing number of studies reported vST activation to be reduced during reward anticipation across severe mental disorders (Arrondo et al., 2015; Hägele et al., 2015; Whitton et al., 2015), for example in MD (Keren et al., 2018; Zhang et al., 2013) and BP (Nusslock et al., 2012), alterations were more compelling and consistent on the psychosis end of the mood-psychosis spectrum (Schwarz et al., 2019). Hereby, vST alterations have been related to positive symptoms (Nielsen et al., 2012; Wotruba et al., 2014) and linked to a reduced differentiation between reward-indicating and neutral cues, a measure of aberrant salience (Kapur, 2003; Radua et al., 2015). While previous fMRI studies on reward processing alterations in SZ mostly focused on the vST in isolation, a large body of work has defined dense cortical and subcortical connections of the vST (e.g., Cox & Witten, 2019) that underpin reward-related behavior. This basic neuroscience information has been linked to the pathophysiology of SZ. Specifically, Grace and colleagues (2016) suggested that impaired hippocampal modulation leads to an abnormal reward (or salience)-related response in the vST through a dopaminergic mechanism (Belujon & Grace, 2015; Chergui et al., 1993; Grace, 2010, 2012; Grace & Bunney, 1984; Mayer et al., 1984; Wolfram Schultz, 2016b), which was also highlighted as a druggable circuit in a recent review (Kätzel et al., 2020). Context-dependent regulation of the vST has been related to parvalbumin-expressing GABAergic interneurons in the ventral hippocampus (Grace, 2016), which are reduced in mouse models of SZ (Lodge et al., 2009; Lodge & Grace, 2007) and post-mortem studies in SZ (Benes et al., 1998; Zhang & Reynolds, 2002). While these cellular mechanisms cannot be studied directly in humans in vivo, functional connectivity during fMRI offers a way to study functional interactions of the hippocampal formation. While substantial evidence implicates structural and functional hippocampal alterations in SZ (Haukvik et al., 2018; Heckers, 2001; Heckers & Konradi, 2015; Medoff et al., 2001; Roeske et al., 2020; Silbersweig et al., 1995; Stone et al., 2010), studies of the functional connectivity between the hippocampus and the vST during reward processing are missing. If the theoretical framework outlined above translates to humans, functional interactions between the vST and the hippocampus during reward processing should be altered in patients, be familial, and linked to genetic risk for psychosis. To close this gap, we investigated the functional connectivity

between the vST and the hippocampus during reward processing using a well-established MID task (Kirsch et al., 2003; Knutson et al., 2001) during fMRI in a large, transdiagnostic sample. We further characterized the vST-hippocampus connectivity phenotype by probing the following research questions: First, we investigated whether vST-hippocampus coupling was altered in SZ and whether these alterations are specific for SZ or extend transdiagnostically to mood disorders such as BP and MD. Second, we tested familiality of this phenotype by examining whether unaffected first-degree relatives of patients with SZ, BP and MD show altered vST-hippocampus coupling compared to HC, and whether a low or high functional coupling relates to PGR scores for SZ in HC. Third, we probed the clinical relevance of the identified phenotype by associating vST-hippocampus coupling to behavioral dimensions associated with the three major symptom domains in SZ: positive, negative, and cognitive symptoms. To this end, we extracted factors related to positive and negative symptoms as previously published (Barrantes-Vidal et al., 2013; Raine, 1991). With respect to cognitive dysfunction, we specifically focused on memory functioning, given 1) its significance in psychosis (Fusar-Poli et al., 2012; Thoma et al., 2009), 2) its pivotal role in hippocampal activation (Lisman et al., 2017), structure (Thoma et al., 2009) and connectivity (Avery, Rogers, & Heckers, 2018) and 3) the direct link of parvalbumin-expressing interneurons between the hippocampus and the nucleus accumbens shown to affect memory function in rodents (Trouche et al., 2019). Dimensional analyses were done across all groups, thereby exploring the full range of symptom domains from health to disease (Cuthbert, 2014; Insel et al., 2010).

2.2.3 Methods

Sample

We assessed 730 participants, including healthy individuals, unaffected first-grade relatives and affected patients with SZ, BP, and MD (see Table 2.4). Data were collected in two acquisition waves (1: 2008-2012; 2:2014-2018) at the Central Institute of Mental Health in Mannheim, the Medical Faculty of the University of Bonn, and the Department of Psychiatry and Psychotherapy at Charité-Universitätsmedizin Berlin. All participants provided written informed consent for protocols approved by the institutional ethics review boards at each site. Psychological assessments included the schizotypal personality questionnaire (SPQ) (Raine, 1991) to assess individual schizotypy levels and the verbal learning memory test (VLMT) (Helmstaedter et al., 2001) to assess individual memory performance (see Table 2.4).

Comparison to previous publication: Compared to our recent publication (Schwarz et al., 2019), we used a larger sample ($N_{current}$ = 730 vs. $N_{previous}$ = 221), included first degree relatives with SZ (already published in Grimm et al. (2014)), BP and MD and used a different version of the MID task, which also includes a loss-avoidance condition.

Diagnostic evaluation: Psychiatric diagnoses were confirmed by trained clinical interviewers using the German version of SCID-I (First et al., 2001). Patients with BP type 2 were excluded. Current symptom severity was assessed using the PANSS (Kay et al., 1987), the YMRS (Young et al., 1978) and the HAM-D (Hamilton, 1967). In addition, general disorder severity was rated using the CGI (Guy, 1976) across all patient groups (see Table 2.4).

Comorbidities: As nearly half of the patients with psychiatric disorders fulfill the criteria of at least one more mental disorder (Kessler et al., 2005), we followed the recommendations of Greene (2016) and didn't exclude patients with a lifetime or concurrent comorbid psychiatric diagnosis (see Table S2.11). However, patients were only included if comorbidities 1) evolved as a consequence of or 2) were markedly less pronounced as the primary disorder, as evaluated in the clinical interview. In addition, patients reporting a lifetime diagnosis of substance dependence or personality disorder were excluded. The main reason to exclude patients with profound axis II disorders was because axis II disorders evolve early in life (First et al., 2001) and aggravate or even cause axis I disorders instead of evolving as a consequence of axis I disorders (Links & Eynan, 2013). Regarding substance dependence, a lifetime diagnosis has been associated with alterations in the mesolimbic reward network during reward anticipation (Luijten et al., 2017), which is a major confound in the current investigation.

Medication: In order to address the possibility of a confounding effect of current medication status, we used CPZ-e and further computed an index of medication load following the procedure outlined by Hassel and colleagues (2008) (see Table 2.4). For every substance we coded the dosage as *absent* = 0, *low* = 1, or *high* = 2 and computed a sum score for all substances. Antidepressants and mood stabilizers were coded as high vs. low based on the rating scores published by Sackeim (2001). For antipsychotic medication, the mean ED50 for CPZ-e was used to distinguish between high and low. Note that information about detailed medication doses were only available for a subset of patients recruited in Mannheim (see Table S2.11).

Table 2.4: Sample description.

Group	HC	SZ_{Rel}	BP_{Rel}	MD_{Rel}	SZ_{Pat}	BP_{Pat}	MD_{Pat}	Between-group differences
N	397	46	51	86	45	45	60	
Bonn	130	14	29	32	-	-	-	
Mannheim	142	17	10	28	25	20	30	
Berlin	125	15	12	26	21	25	30	
Age	32.14 (10.3)	31.91 (12.5)	29.43 (10.1)	27.83 (9.2)	33.62 (10.0)	33.04 (9.3)	34.30 (11.7)	$F_{(6,723)} = 3.560$, $p < .002$
Sex (m/f)	190/207	16/30	21/30	32/54	29/16	20/25	19/41	$\chi^2_{(6)} = 16.853$, $p = .010$
Frame-wise Displacement	.19 (.07)	.19 (.08)	.18 (.08)	.17 (.06)	.25 (.08)	.20 (.07)	.21 (.08)	$F_{(6,723)} = 6.048$, $p < .001$
Medication value (Mannheim only)	-	-	-	-	2.50 (2.5)	2.77 (1.3)	1.75 (1.4)	$F_{(2,69)} = 2.469$, $p = .092$
CPZ-e (Mannheim only)	-	-	-	-	390.75 (337.2)	142.00 (206.5)	19.40 (49.8)	$F_{(2,69)} = 13.561$, $p < .001$
CGI	-	-	-	-	4.24 (1.1)	3.72 (1.0)	3.93 (1.2)	$F_{(2,138)} = 2.395$, $p = .095$
PANSS	-	-	-	-	52.51 (14.6)	41.84 (10.4)	44.65 (8.4)	$F_{(2,143)} = 10.866$, $p < .001$
HAM-D	-	-	-	-	6.64 (3.9)	7.47 (6.0)	13.27 (6.5)	$F_{(2,144)} = 20.985$, $p < .001$
YMRS	-	-	-	-	0.78 (1.26)	3.96 (5.0)	0.59 (1.1)	$F_{(2,141)} = 17.601$, $p < .001$
SPQ	8.54 (7.9)	9.40 (9.3)	10.04 (7.5)	11.13 (9.7)	26.88 (14.1)	26.5 (14.5)	22.70 (12.6)	$F_{(6,696)} = 55.262$, $p < .001$
VLMT	60.72 (7.7)	58.33(7.0)	59.37 (9.7)	60.75 (7.9)	52.69 (10.1)	58.49 (9.1)	60.17 (6.4)	$F_{(6,712)} = 7.531$, $p < .001$

Displayed are mean values (standard deviation) or numbers (site; sex) and statistical between-group comparisons. For nonparametric test, we used the Kruskal-Wallis test (df = 5); for parametric tests, analysis of variance was computed. Abbreviations: HC: healthy control; SZ: schizophrenia; BP: bipolar disorder, MD: major depression; m: male; f: female; CPZ-e: chlorpromazine dose equivalents; CGI: Clinical Global Impression Scale (Guy, 1976) (1: no mental disorder – 7: extreme mental disorder); PANSS: Positive and Negative Symptom Rating Scale (Kay et al., 1987); HAMD-D: Hamilton Depression Scale (Hamilton, 1967); YMRS: Young Mania Rating Scale (Young et al., 1978); SPQ: schizotypal personality questionnaire (Raine, 1991); VLMT: verbal learning memory test (Helmstaedter et al., 2001).

First-degree relatives: Relatives were included if they had one or more first-degree relative with the respective diagnosis, and no personal and familial history of other mental disorders, as confirmed using the SCID-I-Interview (First et al., 2001), or by medical reports.

Exclusion criteria: None of the subjects reported any history of neurological or significant general medical conditions including liver, cardiac, or renal dysfunctions, a history of head trauma or pregnancy.

Neuroimaging paradigm

We used a well-established MID task during fMRI and four conditions (win, loose, neutral, and verbal; see Figure 2.5). Subjects were asked to give a speeded response (button press) to a visual target (brief light flash) presented on a screen. In the reward trials a vertical arrow pointing upwards indicated the possibility to earn 2€, whereas a vertical arrow pointing downwards indicated the chance of avoiding to lose 2€ if responses were given within a predefined response time window. No reward option was given in verbal and neutral trials (control condition). In the verbal trials (double-headed vertical arrow) participants perform the same task but only get a visual feedback ("you reacted fast!" or "you reacted slow!"), whereas in the neutral condition (double-headed horizontal arrow) no visual target and no speeded response was required. At the end of each trial, the balance of money won and lost so far was shown. In total, 10 trials for every condition were presented in a pseudorandomized order. The response time window was continuously adapted to ensure a comparable number of reward events across subjects and groups (i.e., a 5 % increase after slow responses and a 5 % decrease after fast responses). While groups showed significant group differences in reaction time ($F_{(6,718)} = 2.768$, $p = .011$), with HC reacting faster compared to patients with SZ and relatives with MD ($p < .05$), these differences were not reflected in the overall outcome (number of win trials; $F_{(6,718)} = 0.999$, $p = .425$) suggesting that subjects understood the task equally well and experienced a similar rewarding effect of the task.

QC parameters

Head motion parameters were quantified as previously detailed (Grimm et al., 2014; Plichta et al., 2012; Yan et al., 2013) and included the maximal volume-to-volume translational excursions across the time series, the maximal volume-to-volume rotational excursions across the time series, and mFD (Power et al., 2012). The number of spikes, signal-to-noise, signal-to-fluctuation

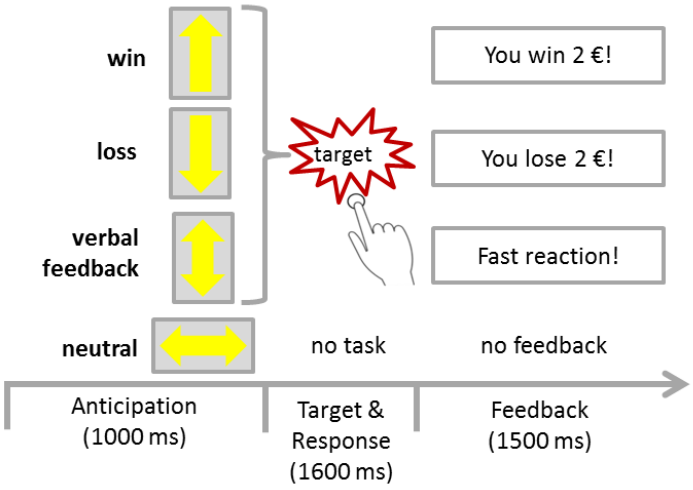

Figure 2.5: Reward anticipation task. Subjects were asked to give speeded responses to a visual target (brief light flash). Preceding cues indicated whether subjects have the chance to win or avoid losing 2 Euros (reward conditions), getting a feedback (verbal condition) or just watch (neutral condition).

and signal-to-ghost ratio of images was calculated using the New York University Center for Brain Imaging data Quality toolbox (Friedman & Glover, 2006; Simmons et al., 1999; Weisskoff, 1996).

Statistical comparisons of data quality parameters between the groups were performed with SPSS (IBM, SPSS, version 27) using univariate ANCOVA, including diagnosis as factor of interest and age, sex, site and acquisition wave as covariates of no interest (see Table S2.12).

MRI data acquisition and preprocessing

Magnetic resonance imaging was performed on three comparable 3T Siemens Trio scanners (Erlangen, Germany) using identical scanning protocols in Mannheim, Berlin and Bonn. Scanners were equipped with a 12-channel head coil. Functional images were acquired using an EPI sequence (TE: 30 ms, TR: 2 s, α: 80°, matrix: 64 × 64, FOV: 192 × 192 mm, in-plane resolution: 3 x 3 mm, slice thickness: 4 mm, gap: 1 mm, 28 axial slices, 267 volumes). Image preprocessing followed standard processing routines in SPM12 (Wellcome Centre for Human Neuroimaging, n.d.), including a two-pass realignment procedure, slice time correction, registration of the functional mean image to the MNI template and spatial normalization into standard stereotactic space, application of resulting normalization parameters to the functional time series, resampling to 3 mm isotropic voxels, and smoothing with an 8 mm full-width at half-maximum Gaussian Kernel. As previously described, datasets with more than 20% of frames exceeding 0.5 mm FD were excluded (Schwarz et al., 2019).

First-level analyses

Activation analyses: In line with our previous study (Grimm et al., 2014), functional activation during reward anticipation was assessed as differential response to win and lose cues as compared to neutral and verbal cues. To this end, the six task regressors (win, loose, verbal, neutral, target and feedback) were modeled as stick functions, convolved with a canonical HRF, and entered into a first-level GLM, along with six session-wise motion regressors derived from the realignment step. At the model estimation stage, a high-pass filter with a cutoff of 128 seconds and an autoregressive model of the first order were applied. Contrast images (contrast: [win + loss] > [verbal + neutral]) were created and subjected to second-level statistical analysis.

Connectivity analyses: We assessed functional connectivity of the vST using a seeded connectivity approach. For each subject, we extracted the first eigenvariate of the time series in the right vST using a 6mm-sphere centered at the peak voxel of the main effect of group [x = 12, y = 20, z = -4]. Given the larger task and group effects in the right compared to the left vST, we decided to investigate vST connectivity in the right hemisphere which is in line with our previous publication (Schwarz et al., 2019). The time series was adjusted for effects of interest (i.e., removal of nuisance variables) and subjected to first-level GLMs, along with the following regressors of no interest: (1) movement parameters from the realignment step, (2) first eigenvariates derived from cerebral spinal fluid and white matter masks and (3) regressors encoding for the experimental conditions. Model estimation was performed as outlined above. The resulting beta image was subjected to second-level analyses.

Phenotype identification: group differences in vST brain activation and vST-hippocampus connectivity

We conducted between-group analyses on individual contrast images for activation and functional connectivity using full-factorial designs with diagnostic group (HC, SZ_{Rel}, BP_{Rel}, MD_{Rel}, SZ_{Pat}, BP_{Pat}, MD_{Pat}) as between-subject factor. Age, sex, site, acquisition wave, and head motion (mFD) were included as covariates of no interest. In case of a significant main effect of group, F-tests were followed up by post-hoc t-tests where patient and relative groups were compared to HCs. In line with our hypothesis of aberrant vST activation (Hägele et al., 2015) and vST-hippocampus connectivity (Grace, 2016) significance was defined as $p < 0.05$, FWE corrected within well-established a priori defined masks of the vST and the hippocampus. In line with our previous work (Plichta et al., 2012; Schwarz et al., 2019) the vST mask was composed of the “caudate head” taken

from the WFU-PickAtlas (Maldjian et al., 2004, 2003) and the "accumbens" mask from the Harvard-Oxford Subcortical Structural Atlas (Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006) whereas the hippocampus mask based on the automated anatomical labelling atlas (Tzourio-Mazoyer et al., 2002).

In order to probe the transdiagnostic relevance of the identified phenotype for psychosis, we additionally separated patients based on reported current psychotic symptoms (PANSS positive scale (Kay et al., 1987); cutoff score: 10) into a low (N = 56) and high (N = 90) psychosis group and tested whether the extracted vST-hippocampus coupling estimates differed between the two patient populations.

In order to target the potentially confounding effect of medication (Abler et al., 2007; Stoy et al., 2012), we investigated whether the standardized composite medication values or CPZ-e levels were related to second-level peak voxel estimates using partial correlation analyses implemented in SPSS (IBM, SPSS, version 27) while controlling for age and sex.

Genetic underpinnings: vST-hippocampus coupling and PGR scores for SZ

PGR score calculation: In order to further validate our intermediate phenotype, we used a PGR approach in a subset of HC subjects (N = 295, mean age: 32.1 ± 9.8 years, 154 males).

Genotyping QC, imputation, and relatedness test: Infinium PsychArray BeadChip by Illumina ("PsychChip") was used for genotyping samples. The chromosome Y and the mitochondrial DNA SNPs were not considered. For all given samples, standard QC and imputation are performed using Gimpute pipeline (Chen et al., 2019). The following QC steps were applied: 1) Remove male subjects with more than 10 haploid heterozygous SNPs on chromosome X; 2) Remove SNPs with missing genotyping rate > 5%; 3) Exclude samples with missingness >= 0.02; 4) Exclude samples with autosomal heterozygosity deviation |Fhet| >= 0.2; 5) Remove SNPs with the proportion of missing genotyping > 2%; 6) If controls existed in the dataset, remove SNPs with difference in SNP missingness between cases and controls >= 0.02; 7) Remove SNPs if the Hardy-Weinberg equilibrium exact test P-value was < 1 x 10-6 in controls. Imputation was carried out using IMPUTE2/SHAPEIT (Delaneau et al., 2013; Howie et al., 2012; Howie et al., 2009), which chooses a European reference panel for each study sample in each 3 Mb segment of the genome. This imputation reference set is from the full 1000 Genome Project dataset (August 2012, 30,069,288 variants, release "v3.macGT1"). The length of buffer region is set to be 500 kb on either side of each segment. All other parameters were set to default values implemented in IMPUTE2. After

imputation, SNPs with high imputation quality (INFO >= 0.6) and successfully imputed in >= 20 samples were retained. The proportion of alleles shared identity-by-decent estimated using PLINK was used to identify relatedness for all pairs of samples (Stevens et al., 2011). The following criteria were used to select a subset of autosomal SNPs for relatedness testing: 1.) SNPs from the MHC region were excluded (chr6:28,477,797-33,448,354); 2.) SNPs were pruned based on linkage disequilibrium (r2 > 0.02 within 50 variant windows); 3.) SNPs with minor allele frequency (MAF) < 0.05 were removed. A threshold of $\hat{\pi} > 0.2$ was used to identify related pairs of samples and exclude one member of each pair at random. Using the same set of autosomal SNPs, we determined principal components to be used as covariates during downstream analyses.

PGR score calculation: The schizophrenia PGR score was computed using Psychiatric Genomics Consortium summary statistics taken from Schizophrenia Working Group of the Psychiatric Genomics (Ripke et al., 2014) following the method developed by Purcell and colleague (Purcell et al., 2009) and using the PRSice software (Euesden, Lewis, & O'Reilly, 2015). Briefly, PGR scores were calculated by summing schizophrenia-associated alleles, weighted by the natural log of the odds ratio. To ensure that SNPs were not in high linkage disequilibrium (LD) with one another, clumping was applied on the genotype data using an LD r2 threshold of 0.1 and a genomic distance threshold of 250 kb. PGR scores were constructed based on genome-wide significant variants ($p = 5x10^{-8}$).

PGR scores in high vs. low vST-hippocampus couplers: We used a median split to group healthy subjects according to their vST-hippocampus connectivity in low (N = 148) and high couplers (N = 147). We subsequently performed ANCOVA analyses including coupling-group as covariate of interest and age, sex, site, mFD, acquisition wave and the first 10 principal components extracted from genome-wide association data as covariates of no interest.

vST-hippocampus coupling and symptom domains of SZ

Proxies of positive, negative and cognitive symptoms: To probe for clinical relevance, we associated vST-hippocampus coupling to traits related to positive, negative and cognitive symptoms. Factors for positive and negative symptoms were extracted from a PCA implemented in SPSS (IBM, SPSS, version 27) using the nine sub scores of the SPQ (Raine, 1991) (see Table S2.13). We first tested whether the SPQ sub scores were suitable to perform PCA (Streiner, 1994). Individual data were checked for completeness and missing values (less than 5%) were imputed using the mean of the remaining values. We then computed the Kaiser-Meyer-Olkin measure of

sampling adequacy. The resulting value of 0.87 was well above the commonly recommended minimum value of 0.6. In addition, we computed the Bartlett's test of sphericity which indicated that included variables differed sufficiently from each other ($\chi^2_{(36)} = 2831.797$, $p < .001$). Subsequently, PCA was applied to identify underlying patterns of coherence among the included variables. As expected (Barrantes-Vidal et al., 2013), the factor analysis resulted in two variables with an eigenvalue greater than 1 explaining 64 % of the total variance. Finally, we applied varimax rotation in order to simplify the interpretation of the factors. Commonalities and factor loadings of all included measures and subscales are outlined in Table S2.13. As expected (Barrantes-Vidal et al., 2013), this revealed two uncorrelated factors ($SPQ_{positive}$ and $SPQ_{negative}$) covering aspects of negative (e.g., blunted affect, lack of close friends) and positive symptoms (e.g., magical thinking, ideas of reference). The SPQ enables the investigation of psychotic-like experiences in the general population and has consistently been related to SZ on a genetic, behavioral and neurobiological level (Raine, 1991). The validity of the $SPQ_{positive}$ and $SPQ_{negative}$ factors was confirmed by their significant association with the respective sub scales of the PANSS (Kay et al., 1987) in patients $SPQ_{positive}$: $r = .324$, $p < 001$; $SPQ_{negative}$: $r = .184$, $p = .026$; see Figure S2.7). For the association between vST-hippocampus coupling and cognitive functions related to memory, we used the VLMT (Helmstaedter et al., 2001) to assess verbal short-term memory performance.

Group differences of $SPQ_{negative}$, $SPQ_{positive}$ and VLMT scores: Overall groups differed with respect to their individual level on $SPQ_{positive}$, $SPQ_{negative}$ and VLMT levels ($SPQ_{negative}$: $F_{(6,717)} = 25.668$, $p < .001$, see Figure S2.8 and $SPQ_{positive}$: $F_{(6,717)} = 23.417$, $p < .001$ as well as VLMT: $F_{(6,706)} = 6.008$, $p < .001$, see Figure 2.8). Specifically, $SPQ_{negative}$ values were higher in patients compared to HC and all first-grade relative groups (all $p < .001$). Moreover, patients with SZ showed lower scores compared to patients with MD ($p = .001$) and BP ($p = .026$). Similarly, $SPQ_{positive}$ values were higher in patients with SZ and BP compared to HC and all first-grade relative groups (all $p < .001$). Moreover, patients with SZ showed higher scores compared to patients with MD ($p < .001$) and BP ($p = .001$) and patients with BP had higher scores compared to MD patients ($p < .001$) but lower scores compared to SZ patients ($p = .002$). With respect to individual memory performance, patients with SZ showed a lower performance to all other groups (all $p < .05$). In addition, first-degree relatives with SZ and patient with BP showed lower VLMT values compared to HC (SZ_{Rel} vs. HC: $p = .014$; BP_{Pat} vs. HC: $p = .048$).

Association of symptom domains and vST-hippocampus coupling: We included individual $SPQ_{positive}$, $SPQ_{negative}$ and VLMT levels as covariates of interest in separate one-sample t-tests on

vST brain connectivity along with the above-named covariates of no interest. The same statistical thresholds were applied as outlined above. In addition, we tested whether individual $SPQ_{positive}$, $SPQ_{negative}$ or VLMT levels were predictive of vST-hippocampus coupling beyond the effect of diagnostic category as outlined previously (Schwarz et al., 2019) (see below).

Post hoc analyses of dimensional measures: In order to probe the clinical significance of the identified phenotype, we associated vST-hippocampus coupling to transdiagnostic and intra-individual differences in clinically relevant traits related to positive and negative symptoms (see above) as well as cognitive (memory) performance. We first included individual positive and negative SPQ as well as VLMT levels as covariates of interest in separate one-sample t-tests on vST brain connectivity along with the above-named covariates of no interest. The same statistical thresholds were applied as outlined above. In a second analysis step we tested whether individual symptom levels were predictive of vST-hippocampus coupling beyond the effect of diagnostic category as outlined previously (Schwarz et al., 2019). In short, we extracted peak-voxel estimates within significant activation clusters and used these measures as dependent variables in post-hoc multiple regression analyses. We converted the variable coding for the seven diagnostic groups into six dummy variables using the HC group as the reference category. We included the resulting variables together with the dimensional factors and our covariates of no interest as independent variables into the regression model.

2.2.4 Results

Phenotype Identification: group differences in vST brain activation and vST-hippocampus connectivity

vST-brain activation: We detected group differences in bilateral vST brain activation during reward anticipation in the main effect of group (p_{FWE}<.05, SVC, Figure 2.6a, Table 2.5). Post-hoc tests indicated that compared to HC, vST activation was reduced in patients with SZ and BP as well as in unaffected SZ-relatives (see also Grimm et al. (2014)) (p_{FWE}<.05, SVC), but not in MD-patients, BP-relatives or MD-relatives (see Table S2.14).

vST-hippocampus coupling: In line with the dopamine dysregulation model in SZ (Grace, 2016), we detected group differences in vST-seeded connectivity with the left hippocampus during reward processing (main effect of group: p_{FWE} <.05, SVC, Figure 2.6b). Similar to the activation analyses, post-hoc tests indicated that compared to HC, vST-hippocampus coupling was reduced in patients with SZ and BP and in unaffected SZ-relatives (p_{FWE}< .05, SVC), but not in MD-patients, BP-relatives

or MD-relatives (see Table S2.14). In addition, patients with psychotic symptoms showed lower vST-hippocampus coupling compared to patients with low levels of psychotic symptoms ($F_{(1,140)}$ = 5.652, p = .019; see Figure S2.9). Activation and connectivity results were not modulated by medication values (all p > .05; see Table S2.15).

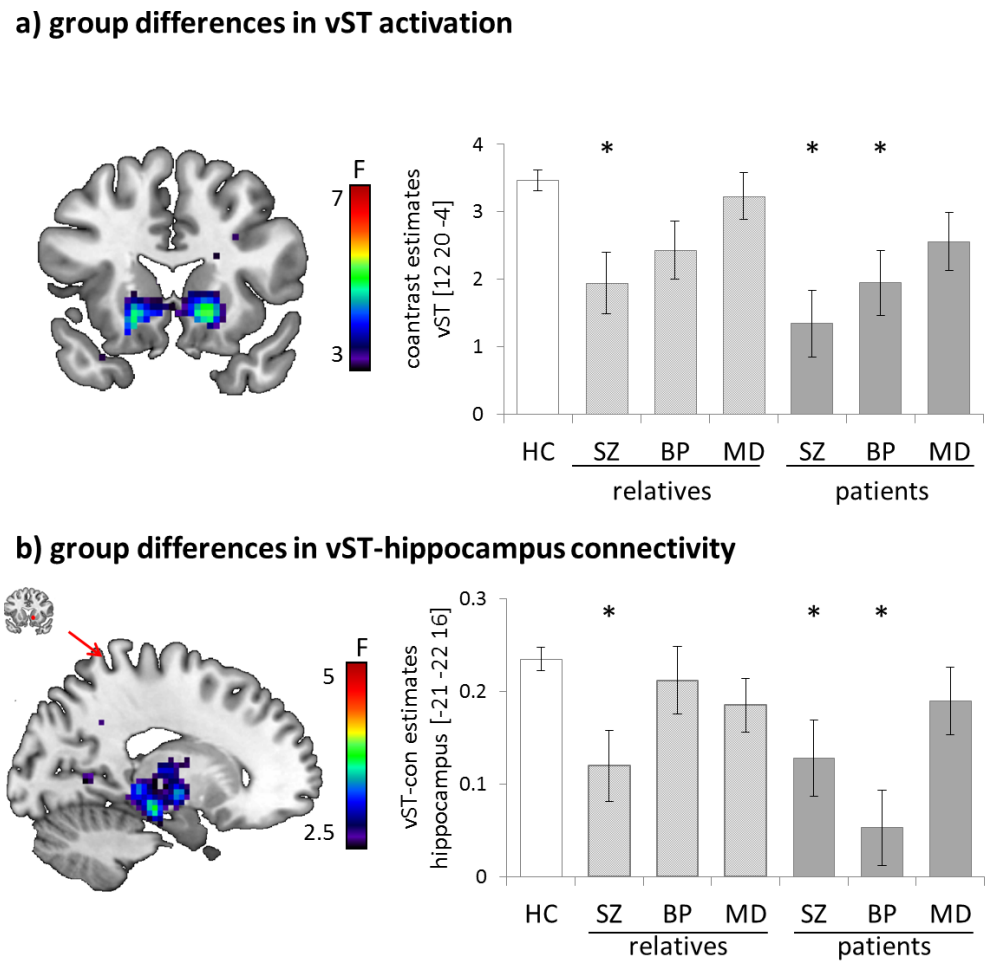

Figure 2.6: Group differences in a) vST brain responses and b) vST-hippocampus connectivity. Left: Depiction of the main effect of group in a) the bilateral vST during reward anticipation (reward > control) and b) the vST-hippocampus connectivity during reward processing**.** For illustration purposes, a significance threshold of p_{uncorr} < .005 was applied. Right: Plotted contrast estimates (mean, SE) of the peak voxel in the right vST (a) and left hippocampus (b). *indicates significance compared to healthy control (HC) group. SZ: schizophrenia, BP: bipolar; MD: major depression, vST: ventral striatum.

Table 2.5: Group differences and dimensional associations.

Region	k	x	y	z	*F/T*	p_{corr}
GROUP DIFFERENCES:						
vST activation						
ventral striatum R	42	12	20	-4	5.55	.001
ventral striatum L	35	-9	20	5	4.47	.008
vST-hippocampus coupling						
hippocampus L	20	-18	-25	-10	4.60	.026
DIMENSIONAL ASSOCIATIONS (vST-connectivity):						
$SPQ_{positive}$						
hippocampus L	82	-15	-10	-16	3.72	.016
hippocampus R	20	27	-31	-4	3.72	.016
VLMT						
hippocampus R	83	30	-34	-1	3.68	.020
hippocampus L	60	-24	-34	-7	3.43	.045

Cluster extent *k* is given at $p_{corr} < .05$, family wise error corrected for multiple comparisons within the relevant regions of interest using small volume correction for multiple comparisons. X-, y-, and z-coordinates (MNI) and statistical information refer to the peak voxel(s) in the corresponding cluster. R: right, L: left, vST: ventral striatum, SPQ: schizotypal personality questionnaire (Raine, 1991); VLMT: verbal learning memory test (Helmstaedter et al., 2001).

Genetic underpinnings: vST-hippocampus coupling and PGR scores for SZ

As expected, healthy subjects with a low vST-hippocampus coupling had higher PGR scores for SZ compared to subjects with a high coupling ($F_{(1,277)} = 4.467$, $p = .035$, see Figure 2.7).

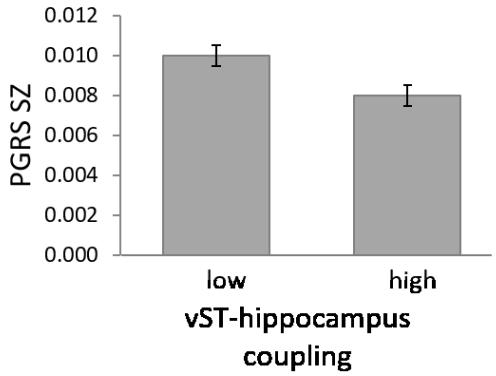

Figure 2.7: Genetic underpinnings of vST-hippocampus connectivity. Polygenic risk scores (PGRS) (mean, SE) of schizophrenia (SZ) in healthy control subjects (N = 295) with high vs. low vST-hippocampus coupling. vST: ventral striatum.

Clinical relevance: vST-hippocampus coupling and symptom domains of SZ

Higher $SPQ_{positive}$ values related to lower vST-seeded connectivity with the bilateral hippocampus across diagnostic groups ($p_{FWE} < .05$, SVC; Figure 2.8, Table 2.5) whereas no significant results emerged for $SPQ_{negative}$ values. Moreover, memory performance was positively associated with bilateral vST-hippocampus connectivity ($p_{FWE} < .05$, SVC; Figure 2.8, Table 2.5).

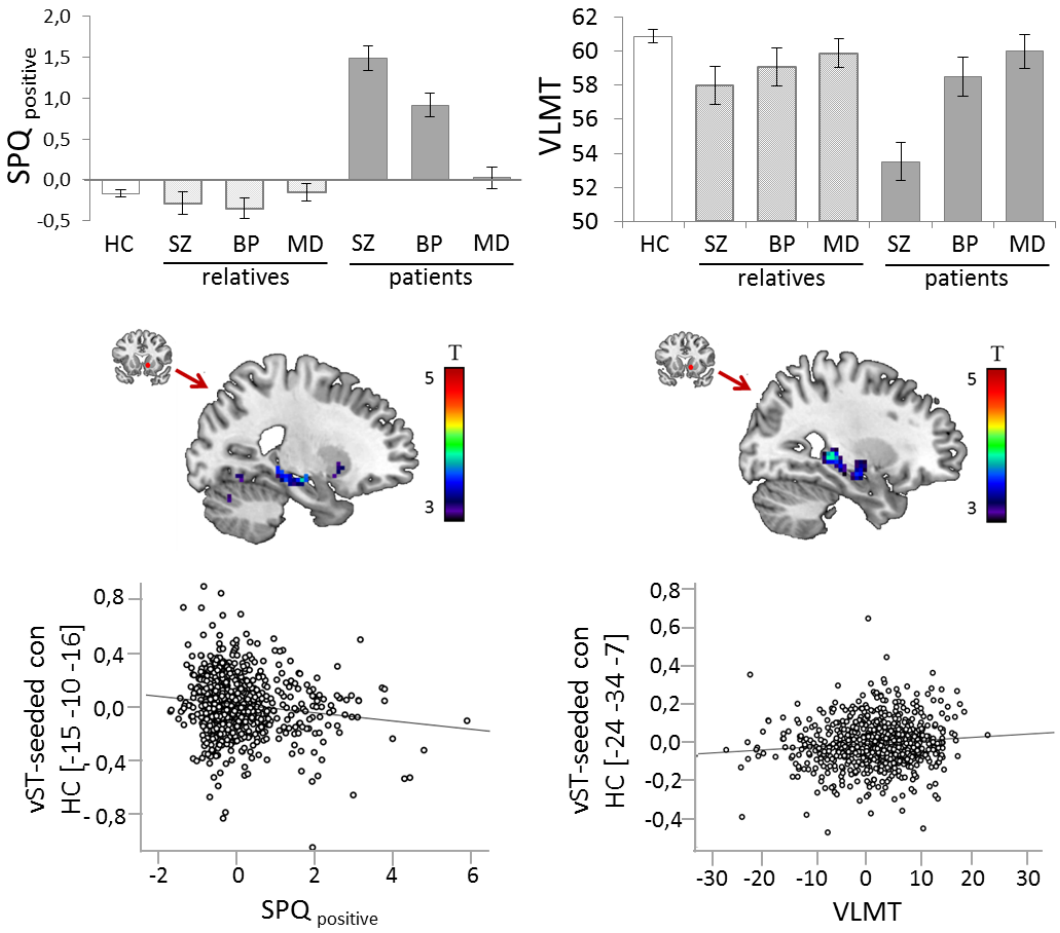

Figure 2.8: Dimensional Results. Top row: group differences (mean, SE) in positive psychotic-like experiences extracted from the schizotypal personality questionnaire ($SPQ_{positive}$) (Raine, 1991); and memory functioning assessed with the verbal-learning memory test sum scores (VLMT) (Helmstaedter et al., 2001). Middle row: Transdiagnostic associations between vST-hippocampus coupling and the $SPQ_{positive}$ (left) and the VLMT (right). For illustration purposes, a significance threshold of $p_{uncorr} < .005$ was applied. Bottom row: Scatter plots display the partial correlation results between $SPQ_{positive}$ (left) as well as VLMT (right) and peak voxel contrast estimates in the vST-hippocampus coupling. r: Pearson correlation coefficient (controlled for diagnostic group, age, sex, site, mean frame-wise displacement and acquisition wave); con: connectivity; HC: healthy controls; SZ: schizophrenia; BP: bipolar; MD: major depression.

Post-hoc analysis of positive SPQ and vST-hippocampus coupling: Multiple regression analyses indicated that the above outlined predictors explained 12.9 %of the total variance in the extracted second level peak voxel in the right hippocampus (R^2 = .129; $F_{(13,715)}$ = 8.113, p < .001) and 8.5 % in the left hippocampus (R^2 = .085; $F_{(13,715)}$ = 5.108, p < .001). For the right hippocampus, the positive SPQ (beta = -.100, p = .010), site (1: beta = -.320, p < .001), mFD (beta = - .078, p = .037), and group (HC vs. MD_{Rel}: beta = -.084, p = .030) significantly predicted vST-hippocampus coupling. For the left hippocampus, the positive SPQ (beta = -.079, p = .016), age (beta = -.078, p = .041, sex (beta = -.091, p = .012), site (2: beta = -.130, p = .004), mFD (beta = -.112, p = .004), and group (HC vs. SZ_{Pat}: beta = -.106, p = .017) significantly predicted vST-hippocampus coupling.

Post-hoc analysis of VLMT and vST-hippocampus coupling: Multiple regression analyses indicated that the above outlined predictors explained 8.5 % of the total variance in the extracted second level peak voxel in the right hippocampus hippocampus (R^2 = .085; $F_{(13,704)}$ = 5.001, p < .001) and 5.0 % in the left hippocampus (R^2 = .050; $F_{(13,704)}$ = 2.878, p < .001). For the right hippocampus, VLMT (beta = .127, p = .001), age (beta = .093, p = .016), and site (1: beta = -.124, p = .007; 2: beta = -.242, p < .001), significantly predicted vST-hippocampus coupling. For the left hippocampus, VLMT (beta = .110, p = .006), age (beta = .079, p = .046), site (2: beta = -.110, p = .010) and group (HC vs. SZ_{Pat}: beta = -.103, p = .018; HC vs. BP_{Pat}: beta = -.120, p = .004) significantly predicted vST-hippocampus coupling.

2.2.5 Discussion

We provide the first evidence that vST-hippocampus coupling during reward processing is an endophenotype for psychotic disorders, supporting the model outlined by Grace and colleagues (2016). Our data indicate that vST-hippocampus coupling 1) is specific for psychotic disorders, 2) is familial and related to genetic risk for SZ and 3) is associated transdiagnostically to clinically relevant measures of positive symptoms and memory performance.

vST-hippocampus coupling across nosological boundaries

As a proof of concept and in line with our previous reports (Schwarz et al., 2019), we show blunted vST activation during reward anticipation in patients with SZ and BP, but not MD, providing further evidence to the transdiagnostic relevance of this intermediate phenotype for psychosis (Hägele et al., 2015). Prominent mechanistic theories have indeed linked blunted vST-activation (Buckholtz et al., 2010; Schott et al., 2008; Weiland et al., 2014) to psychotic symptomatology (Kesby, Eyles, McGrath, & Scott, 2018) via deficient modulation by the hippocampus (Grace, 2016). While our

systems-level measure of coupling cannot define underlying cellular processes, our finding aligns with animal models (Lodge & Grace, 2007, 2009; Perez, Shah, Asher, & Lodge, 2013) and post-mortem studies (Heckers & Konradi, 2015) suggesting that (reward-related) alterations in the vST and associated behaviors are related to the functioning of the hippocampus through a dopaminergic mechanism. Consistently, a recent review highlights the pivotal role of the hippocampal-vST-VTA axis for aberrant salience processing in SZ and its potential for the development of novel therapeutic treatments (Kätzel et al., 2020). Our finding extends to the previous evidence provided by imaging research in patients with SZ showing structural and functional alterations in the hippocampus (Haukvik et al., 2018; Heckers & Konradi, 2015; Roeske et al., 2020), the vST (Eickhoff & Müller, 2015; Radua et al., 2015) and the functional connectivity between the two regions with resting-state connectivity (Kraguljac et al., 2016; Sarpal et al., 2015). While future studies have to further unravel the link between cellular abnormalities in the hippocampus, especially a loss of parvalbumin-expressing interneurons, and functional imaging phenotypes like vST-hippocampus coupling, our results highlight the importance of vST-hippocampus coupling in reward processing (Robison, Thakkar, & Diwadkar, 2020) specifically in psychosis.

Genetic underpinnings of vST-hippocampus coupling

We further found that vST-hippocampus coupling could be an intermediate phenotype for SZ, given the observed reductions in unaffected first-grade relatives of SZ patients (see also Grimm et al., 2014). Alterations were specific for SZ, as we did not observe alterations in unaffected first-degree relatives for BP and MD. This suggests that a low functional vST-hippocampus coupling could be related to genetic risk for SZ. This notion is supported by our observation that reduced coupling was related to higher PGR scores for SZ in our healthy control sample. This extends to previous studies associating genetic risk for SZ to structural and functional alterations in the hippocampus (Heckers & Konradi, 2015; Schobel et al., 2013; Smeland et al., 2018). Together, these results indicate that alterations in the functional vST-hippocampus coupling represent a heritable intermediate phenotype for SZ.

Dimensional association of vST-hippocampus coupling and symptom domains for SZ

We further show associations between functional vST-hippocampus coupling and psychosis-relevant traits related to positive and cognitive but not negative symptoms across diagnoses, thereby indicating a dimensional impact of the introduced phenotype on clinically relevant

functions. Specifically, higher $SPQ_{positive}$ scores related to lower vST-hippocampus coupling. This is in line with the theoretical framework outlined above which suggests that deficient hippocampal modulation of vST leads to positive symptoms in SZ (Grace, 2016). Further evidence showed that alterations in hippocampal functioning relate to psychosis level (Silbersweig et al., 1995) and positive symptoms (Schobel et al., 2013). We extend these findings by showing that the functional vST-hippocampus coupling is related transdiagnostically to clinically relevant trait measures related to SZ.

Besides positive symptoms reduced functional vST-hippocampus coupling was also linked to impaired verbal memory performance. This aligns to previous findings implicating the relevance of memory performance for both psychosis and hippocampal functioning (Trouche et al., 2019). Specifically, memory impairment was related to psychotic disorders (Aleman, Hijman, de Haan, & Kahn, 199AD) especially for memory processes that depended on the hippocampus (Achim et al., 2007; Öngür et al., 2006; Weiss et al., 2004). Mechanistically, parvalbumin-expressing interneurons in the hippocampus have been associated with network plasticity and long-term memory consolidation (Ognjanovski et al., 2017). Accumulating evidence further point to a tight interaction between networks implicated in memory and reward processing (e.g., Adcock et al., 2006; Kahn & Shohamy, 2013; Robison et al., 2020). Specifically, reciprocal connections between the hippocampus and the mesolimbic reward system are thought to strengthen memory encoding based on the valence of a stimulus (Russo & Nestler, 2013). Recently, a direct connection from the hippocampus to the nucleus accumbens through parvalbumin interneurons was shown to enable place reward memories in mice (Trouche et al., 2019). Overall, these findings lend further support to the functional and clinical relevance of vST-hippocampus coupling observed in the present study. In addition, they emphasize the sensitivity of a dimensional approach, highlighting the potential of neuroimaging biomarkers in explaining brain-behavior relationships transdiagnostically (Cuthbert, 2014; Insel et al., 2010).

While our diagnosis-related and genetic analyses link alterations in vST-hippocampus coupling to psychotic disorder categories, our dimensional analyses show that brain-behavior relationships extend across nosological boundaries. Thus, a reduction in vST-hippocampus coupling links to positive symptoms and cognitive dysfunctions even when they do not reach the threshold required for a categorical diagnosis of SZ or BP, thereby highlighting the sensitivity of a dimensional approach (Cuthbert, 2014; Insel et al., 2010).

Strengths and limitations

This study faced several challenges common to clinical imaging. We followed established procedures for handling differences in medication and comorbidities (Greene et al., 2016). We further controlled for basic demographic variables throughout analyses and carried out additional analyses that showed that medication level was not related to vST-hippocampus coupling. As stated, we cannot measure underlying neurochemical or cellular processes using BOLD-fMRI. This also means that we cannot prove that the observed coupling reduction is inhibitory. With respect to imaging quality, we carefully balanced our sample for several head motion and signal-quality parameters and included a proxy for head motion (mFD) as covariate across all analyses. However, we acknowledge that we cannot rule out the possibility of unaddressed influences of some of these confounders. In addition, the inclusion of other diagnostic groups known to show alterations in reward processing (e.g., substance-use disorder) as well as larger samples for each disorder would have been desirable but were beyond the feasible scope of the present study. However, despite all methodological challenges, the investigation of different patient and first-degree relative groups in the same study comes with the valuable advantage of ruling out methodological differences when comparing results between diagnostic entities.

2.2.6 Conclusion

In summary, we provide evidence that vST-hippocampus coupling during reward processing is an endophenotype for psychotic disorders and relates to dimensional, behaviorally meaningful measures of positive symptoms and memory performance across the psychiatric spectrum. Besides informing current disorder-specific mechanistic theories of vST dysfunction, our results can inform the development of pharmacological and therapeutic interventions for example by trainings targeting vST-hippocampus connectivity through neurofeedback or by indirect therapeutic interventions that enhance cognitive control abilities in SZ.

2.2.7 Supplemental Information

TABLES

Table S2.11: Medication and comorbidities.

	Mannheim			Berlin		
Group	**SZ**	**BP**	**MD**	**SZ**	**BP**	**MD**
medication						
CPZe	370.18 (399.8)	147.68 (208.7)	19.40 (49.8)	-	-	-
medication load	2.47 (2.5)	2.80 (1.4)	1.75 (1.439)	-	-	-
tricyclic antidepressants	1	0	2	2	0	7
SSRI	4	7	13	2	8	12
other antidepressants	0	2	7	1	5	6
typical antipsychotics	4	0	0	1	1	0
atypical antipsychotics	19	19	6	21	6	3
sedativa	0	0	0	3	1	1
lithium	0	8	2	1	7	0
other mood stabilizers	2	13	2	1	7	2
anticonvulsants	2	13	2	1	7	2
methylphenidate	0	4	0	2	0	0
comorbidities						
alcohol abuse	0	2	3	1	0	0
cannabis abuse	2	3	0	3	1	1
amphetamine abuse	1	0	1	2	0	1
depression	0	0	0	0	0	0
anxiety	0	0	1	2	0	8
other	1	1	1	1	2	4

Displayed are mean values (standard error) and number of cases (comorbidities). HC: healthy control, SZ: schizophrenia, BP: bipolar disorder, MD: major depression, ASD: autism spectrum disorder, CPZe: chlorpromazine equivalents, medication load as described in Hassel and colleagues (2008); SSRI: selective serotonin reuptake inhibitor.

Table S2.12: Group differences in quality parameters.

Group	**HC**	**SZ_{Rel}**	**BP_{Rel}**	**MD_{Rel}**	**SZ_{Pat}**	**BP_{Pat}**	**MD_{Pat}**	**Between-group differences**
N	397	46	51	86	45	45	60	
Movement: Power's FD	0.19 (0.00)	0.19 (0.01)	0.18 (0.01)	0.17 (0.01)	0.25 (0.01)	0.20 (0.01)	0.21 (0.01)	$F_{(6,718)} = 3.28$, $p = .003$
Movement: total translation (mm)	1.04 (0.04)	1.02 (0.13)	1.11 (0.12)	0.91 (0.10)	1.43 (0.13)	1.08 (0.13)	1.10 (0.12)	$F_{(6,718)} = 1.69$, $p = .120$
Movement: total rotation (degree)	0.93 (0.04)	0.88 (0.12)	0.98 (0.10)	0.91 (0.08)	1.15 (0.12)	1.00 (0.12)	1.01 (0.10)	$F_{(6,720)} = 0.60$, $p = .727$
Spikes	2.08 (1.00)	1.86 (3.03)	1.97 (2.89)	2.79 (2.31)	2.20 (3.26)	0.63 (3.23)	1.02 (2.90)	$F_{(6,718)} = 0.21$, $p = .974$
Signal-to-Noise-Ratio	90.89 (0.74)	86.63 (2.26)	86.05 (2.15)	88.05 (1.72)	91.38 (2.43)	94.98 (240)	94.41 (2.16)	$F_{(6,718)} = 1.93$, $p = .073$
Signal-to-Fluctuation-Noise-Ratio	286.73 (4.25)	298.12 (12.92)	296.31 (12.30)	295.60 (9.84)	278.87 (13.88)	278.64 (13.75)	292.33 (12.347)	$F_{(6,718)} = 0.40$, $p = .877$
Signal-to-Ghost-Ratio	19.00 (0.14)	18.43 (0.44)	18.28 (0.41)	19.02 (0.33)	19.61 (0.47)	18.65 (0.46)	18.81 (0.42)	$F_{(6,718)} = 1.19$, $p = .312$

Displayed are mean values (standard error); Rel: relatives; Pat: patients; HC: healthy control; SZ: schizophrenia; BP: bipolar disorder, MD: major depression; FD: frame-wise displacement (Power et al., 2012).

Table S2.13: Principal component analyses on SPQ sub scores.

	Sub scale	Factor 1: $SPQ_{negative}$	Factor 2: $SPQ_{positive}$	Com.
1	Blunted affect	**.826**	.027	.684
2	Lack of close friends	**.819**	.103	.681
3	Social anxiety	**.744**	.166	.581
4	Paranoid ideation	**.693**	**.415**	.623
5	Odd speech	**.660**	**.347**	.556
6	Magical thinking	-.034	**.830**	.689
7	Ideas of reference	.**510**	**.620**	.644
8	Unusual perceptual experiences	.295	**.796**	.720
9	Odd behavior	.**590**	.**452**	.552

Values in bold represent factor loadings > .3. Com.: communalities

Table S2.14: Post-hoc group differences in vST activation and vST-hippocampus connectivity.

Region	k	x	y	z	T	p_{corr}
vST activation						
HC > SZ-patient						
ventral striatum R	70	12	11	-7	4.04	.001
ventral striatum L	50	-9	20	5	3.76	.003
HC > BP-patient						
ventral striatum R	9	12	20	-1	2.93	.042
HC > SZ-relatives						
ventral striatum L	39	-9	17	-7	3.81	.003
ventral striatum R	20	12	20	-4	3.50	.008
vST-hippocampus connectivity						
HC > SZ-patient						
hippocampus L	7	-33	-28	-10	3.15	.043
HC > BP-patient						
hippocampus L	40	-21	-22	-16	4.08	.002
hippocampus R	15	36	-22	-13	3.62	.010
HC > SZ-relatives						
hippocampus L	8	-21	-22	-19	3.12	.047

Cluster extent *k* is given at $p_{corr} < .05$, family wise error corrected for multiple comparisons within the ventral striatum (activation) or hippocampus (connectivity) region of interest for k > 5 voxel. X-, y-, and z-coordinates (MNI) and statistical information refer to the peak voxel(s) in the corresponding cluster. Only contrasts with significant activation effects in comparison to HC are displayed. HC: healthy controls, SZ: schizophrenia, BP: bipolar disorder, MD: major depressive disorder; R: right, L: left.

Table S2.15: Partial correlation analyses between vST activation as well as functional vST-hippocampus connectivity estimates and medication values.

Region	Total medication load (N = 73)		CPZ-e (N = 73)	
	r	*p*	*r*	*p*
vST R	-.165	.176	-.116	.343
vST-hippocampus L	-.035	.776	-.048	.693

r: partial correlation coefficient (controlled for age and sex), CPZ-e: chlorpromazine equivalents, vST: ventral striatum; R: right, L: left.

FIGURES

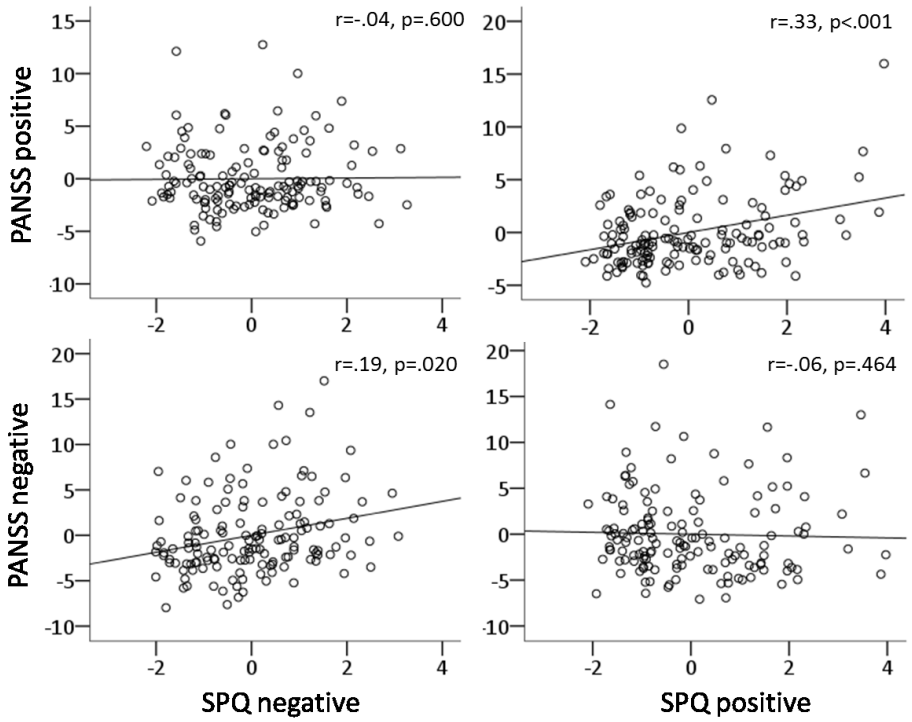

Figure S2.7: Association between SPQ factors and PANSS sub scores. Scatter plots display the partial correlation results between the positive and negative scale of the positive and negative syndrome scale (PANSS) (Kay et al., 1987) and the two factors extracted from a principal component analyses of the nine subscores of the Schiotypical Personality Questionnaire (SPQ) (Raine, 1991), respectivley. r: Pearson correlation coefficient (controlled for age, sex, and site).

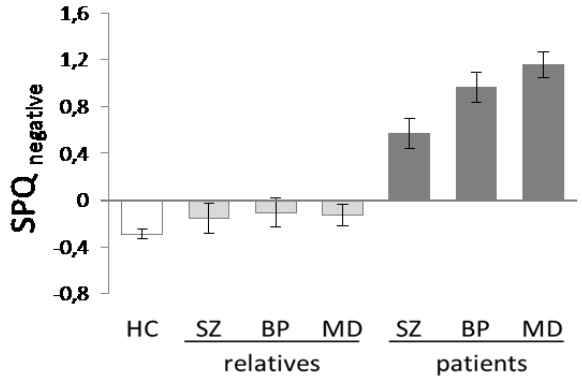

Figure S2.8: Group differences in $SPQ_{negative}$. Values (mean, SE) were extracted from the Schizotypical Personality Questionnaire ($SPQ_{negative}$) (Raine, 1991). HC: healthy controls; SZ: schizophrenia, BP: bipolar, MD: major depression.

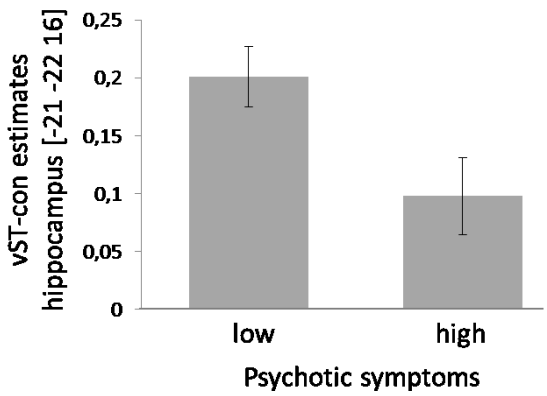

Figure S2.9: vST-hippocampus connectivity differences between patients with high vs. low current psychotic symptoms. Group differences (mean, SE) in ventral striatal (vST)-hippocampus connectivity (con) estimates in patients with high (N = 56) and low (N = 90) psychotic symptoms.

3 DISCUSSION

3.1 Transdiagnostic reward network alterations

3.1.1 Categorical group differences

With respect to research question one, both presented studies found categorical group differences in vST activation during reward anticipation between HC and patient groups in the extended moods-psychosis spectrum. Specifically, compared to HC, reward-related vST activation was blunted in SZ (*hypothesis 1.1*), BP (*hypothesis 1.2*), ASD (*hypothesis 1.4*) but not in MD (*hypothesis 1.3*).

The observed results cannot fully be regarded as a separate replication, because the study samples overlapped between publications. However, study 2 included a much larger sample size (N_{study1} = 221 vs. N_{study2} = 730), as well as unaffected first degree relatives of patients with SZ (also published in Grimm et al., 2014), BP and MD. In addition, two different versions of the MID task were used, adding a social reward condition in study 1 and a loss-avoidance condition in study 2. Thus, while samples were not independent, the consistently observed blunted vST reactivity across different task designs and sample sizes, provide evidence for the transdiagnostic relevance of vST reactivity during reward anticipation.

With respect to SZ, our finding of blunted vST activation is in line with numerous prior studies, including meta-analyses (Chase et al., 2018; Leroy et al., 2020; Radua et al., 2015). Studies in BP and ASD are still rare and provide largely inconsistent results especially in BP (Johnson et al., 2019). Our finding of reduced vST reactivity to reward-indicating cues adds to the yet inconclusive evidence using well-powered patient samples. In contrast to our *hypothesis 1.3* which was based on previous reports (Keren et al., 2018; Zhang et al., 2013), we did not find reduced vST responses in MD patients. This inconsistency bet might result from investigating different reward-related sub-processes. For example, more robust vST activation differences in MD have been observed during reward feedback (Keren et al., 2018). Similarly, Wotruba and colleagues (2014) linked positive symptoms to anticipation-related vST activation whereas negative and depressive symptoms were associated with feedback-related vST reactivity. In addition, differences in medication and state-dependent vST alterations might have contributed to the non-significant group differences between HC and MD (Satterthwaite et al., 2015). However, study 2 showed that

blunted vST reactivity to reward indicating cues was only observed in unaffected SZ-relatives (see also Grimm et al., 2014) but not in relatives of patients with mood disorders. As familial high-risk populations share an enriched set of risk genes without manifest clinical symptoms, confounding factors like medication, illness-duration or current symptom severity are ruled out (Cao, Dixson, et al., 2016; Rasetti & Weinberger, 2011). Overall, our categorical results suggest that reward anticipation is more affected in patients on the psychosis end of the moods-psychosis spectrum, which is in line with a recent PGR study (Lancaster et al., 2016). Future studies are warranted to replicate this dissociation and investigate possible disorder-specific subprocesses during reward processing. At the same time, the exploration of dimensional measures covering general psychological or symptom domains that cut across traditional definitions of health and disease (Cuthbert, 2014; Insel et al., 2010) might help to unravel the underlying biological mechanism of altered reward anticipation.

3.1.2 Dimensional results

The comparison of distinct disorder groups does not allow to infer on underlying shared or distinct biological mechanisms of blunted reward network functioning, therefore transdiagnostic brain-behavioral relationships were investigated as a second research question. Both included studies showed associations of neurocognitive behavioral measures and markers of altered reward network processing. Thereby, in study 1 transdiagnostic vST alterations were related to dimensional measures covering affective (*hypothesis 2.1*), cognitive (*hypothesis 2.2*) and social (*hypothesis 2.3*) functioning.

Interestingly, while no categorical group differences in vST reactivity in MD were detected, our dimensional approach nonetheless suggests that affective instability is associated with vST reactivity across diagnostic groups including MD. As discussed above, this association of dysfunctional regulation of affective symptoms and reward-related vST activation might reflect a diminished attribution of motivational salience to reward-indicating cues (Hägele et al., 2015). While this adds to recent transdiagnostic evidence (Arrondo et al., 2015; Hägele et al., 2015; Satterthwaite et al., 2015), the observed associations between cognitive as well as social functioning and vST brain responses have not been reported before. This might be due to the fact that most studies used single, often disorder-specific clinical measures which show low variance in healthy subjects and focus on single psychopathological processes not considering other psychological variables. However, in line with our results, recent conceptualizations suggest that

different and unrelated processes might lead to reward network alterations, a principle which is referred to as equifinality (Nusslock & Alloy, 2017). Our factor-analytic approach is advantageous because brain-behavior associations are valid for a broad definition of independent functioning domains based on a comprehensive collection of behavioral measures reflecting diverse psychological constructs.

This idea closely follows the HiTOP methodology, which relies substantially on factor analyses and assumes that psychopathology can be described with distinct behavioral dimensions (Kotov et al., 2017). However, the investigated dimensions of social and cognitive functioning are not present in the current HiTOP conceptualization. Given the transdiagnostic relevance of these symptom domains, considering social cognition and cognitive control abilities might improve the validity and comprehensiveness of the approach. In contrast to the HiTOP framework, investigated symptom domains were not hierarchized, which would be an interesting topic for future studies. However, the first factor in our PCA comprises a large collection of clinical measures representing diverse psychological constructs and might resemble the general risk for psychiatric disorders (Jeronimus et al., 2016) reflecting the overall g-factor in the HiTOP conceptualization. These considerations question the interpretation of factor one as a mainly affective (or in the HiTOP language: internalizing) process and rather suggests that it covers the entire spectrum of psychiatric (risk) symptoms. Future studies are warranted to conduct more fine-grained, specifically hierarchical analyses, to investigate whether blunted reward network functioning is related specifically to mood symptomatology or is better reflected by the general degree of impairment.

Overall, our results indicate that different and independent symptom domains, covering affective symptoms but also general cognitive deficits and social functioning abilities, explain variance of brain activation in the vST during reward anticipation across diagnostic boundaries. This suggests that shared and likely multiple processes underlie reward network alterations in psychiatric patients. Similarly, study 2 showed dimensional and transdiagnostic associations between the newly identified vST-connectivity phenotype and clinically relevant measures which are discussed in the following section.

3.2 Beyond the vST: reward-related functional vST-hippocampus coupling as a new endophenotype for psychotic disorders

The third research question investigated a new endophenotype for altered reward processing in psychotic disorders – the functional coupling between the vST and the hippocampus. Thereby,

study 2 showed that the activation of the reward system induced an overall reduction of functional connectivity between the vST and the hippocampus in psychotic but not mood disorders (*hypothesis 3.1*), that 1) was reduced in unaffected first-grade relatives of patients with psychotic but not mood disorders, 2) related to polygenic risk scores for SZ in HC (*hypothesis 3.2*), and 3) is associated with behavioral dimensions of positive (*hypothesis 3.3.1*) and cognitive (*hypothesis 3.3.3*), but not negative symptoms (*hypothesis 3.3.2*).

While study 1 explored alterations of transdiagnostic vST-connectivity patterns and associations between vST activation and independent dimensions of behavioral function, study 2 was strongly hypothesis-driven. We linked the aberrant salience hypothesis (Kapur, 2003; Radua et al., 2015) which has been related to striatal dopamine hyperactivity in SZ (Fusar-Poli & Meyer-Lindenberg, 2013) to the frequently reported impaired functioning of the medial temporal lobe implicated in the glutamatergic regulation of the dopamine system. Structural and functional alterations in the hippocampus are a well-established observation in SZ (Haukvik et al., 2018; Heckers & Konradi, 2015; Roeske et al., 2020). Similarly, altered interactions between the reward network and the hippocampus have been proposed by animal models in SZ (Grace, 2016), post-mortem studies in SZ (Benes et al., 1998; Zhang & Reynolds, 2002), resting-state functional connectivity studies in SZ (Kraguljac et al., 2016; Sarpal et al., 2015), and were recently suggested as a novel circuit-level target for anti-psychotic action (Kätzel et al., 2020). While speculative, the detected reduction of vST-hippocampus coupling might indirectly mirror structural alterations in the hippocampus, specifically the loss of parvalbumin-expressing interneurons, thereby leading to the undifferentiated vST response between reward-indicating and neutral trials. Study 2 further points to a genetic background of the vST-hippocampus phenotype, which is in line with previous findings that linked structural and functional alterations in the hippocampus to the genetic risk for SZ (Heckers & Konradi, 2015; Schobel et al., 2013; Smeland et al., 2018). The specificity of the identified phenotype for psychosis is further supported by the dimensional results which suggest that blunted vST-hippocampus coupling relates to the degree of positive symptoms. Surprisingly and similar to study 1, we also observed associations with cognitive abilities, specifically memory performance, suggesting that multiple mechanisms might underlie the newly identified imaging phenotype. Interestingly, the dimensional analyses show that brain-behavior relationships extend across nosological boundaries, thereby highlighting the sensitivity of a dimensional approach (Cuthbert, 2014; Insel et al., 2010). This suggests that the identified phenotype is not a disorder-specific, but rather a symptom-specific (stratification) biomarker, emphasizing the potential of

shifting our neurobiological understanding of mental disorders towards a more dimensional framework.

Overall, study 2 closely followed the RDoC conceptualization. We focused on one basic domain of human functioning – the Positive Valence System – and investigated a possible intermediate phenotype candidate deduced from preclinical studies, along the full range of human behavior from normal do abnormal across multiple investigation levels (i.e., genomics, neural circuits and behavior). While our systems-level measure of coupling cannot define underlying cellular processes, future studies have to unravel the link between structural abnormalities in the hippocampus and functional imaging phenotypes like vST-hippocampus coupling. This introduced vST-hippocampus coupling phenotype will not directly change our diagnostic system, but it might add substantial value for etiological models of aberrant salience processing, potentially informing the development of new treatment options as discussed below.

3.3 Cognition and large-scale executive network alterations – an overarching and neglected symptom domain?

Surprisingly, both studies presented here revealed associations between blunted reward network functioning and indicators of cognitive performance measures (i.e., general cognitive functioning and memory performance) highlighting the role of cognitive abilities for transdiagnostic reward network alterations. Traditionally, differences in cognitive performance are regarded as a confounding factor and in consequence, cognitive functioning is included as a covariate of no interest. For example, Dowd et al. (2012) argued that instrumental incentive delay tasks might be confounded with deficits in response selection and execution and showed absent group differences between SZ and HC using a passive viewing paradigm, which is less cognitive demanding (Dowd & Barch, 2012). However, both presented studies showed that symptom-related measures like affective instability (study 1) and schizotypy (study 2) were associated with reward network functioning besides cognitive performance. It is unlikely that intelligence differences alone can explain the substantial evidence indicating behavioral and neural reward-related alterations across psychiatric conditions (Arrondo et al., 2015; Hägele et al., 2015; Whitton et al., 2015).

Moreover, cognitive deficits might also directly contribute to behavioral symptoms and intermediate imaging phenotypes, such as blunted vST reactivity, possibly resembling an underlying etiological mechanism. This idea is at the heart of a transdiagnostic neurocognitive

theory introduced by Cole and colleagues (2014), which suggests that cognitive control is a domain- and disorder-unspecific pathophysiological mechanism in psychiatric conditions. The authors argue that the capacity and flexibility of large-scale control networks, such as the FPN, is compromised in psychiatric conditions (Cole et al., 2014). The experience and regulation of symptoms (e.g., depressed mood or ideas of reference) consumes cognitive resources, which are no longer available for the current task and lead to domain-specific deficits, such as a diminished motivational reacting to reward-indicating cues. This aligns to our observation of transdiagnostic alterations in the functional connectivity between the vST and fronto-parietal executive control regions (*hypothesis 2.4*). The investigation of the transdiagnostic and intermediate role of cognitive functioning in the context of reward processing is of specific interest since cognitive functioning is highly heritable (Bouchard, 2014; Deary, Johnson, & Houlihan, 2009; Deary, Penke, & Johnson, 2010; Haworth et al., 2010; Plomin & Deary, 2015), plays a pivotal role in reward processing (Braver et al., 2014; Pessoa, 2015) and is impaired across psychiatric conditions (Trivedi, 2006) as well as in their first-degree relatives (e.g., Calafiore, Rossell, & Van Rheenen, 2018; Seidman et al., 2015). Moreover, genome-wide association studies as well as PRS approaches suggest an overlap between genetic contributions to psychiatric disorders along the moods-psychosis spectrum and measures of intelligence (Dickinson et al., 2014; Hagenaars et al., 2016; Hellard et al., 2017; Hubbard et al., 2016; Lencz et al., 2014; Savage et al., 2018; Smeland et al., 2017; Van Os et al., 2017). It is surprising that little is known about the role that cognition plays for the well-established striatal intermediate phenotype.

3.4 Critical reflection and limitations in clinical fMRI studies

When using neuroimaging techniques in clinical populations specific considerations are needed with respect to data collection, subject inclusion and overall data quality.

3.4.1 Subject Selection

One major challenge comes with the inclusion of subjects. Our categorical approach focuses on group differences between specific and distinct patient populations. In order to increase the internal validity of the study design, “clean” patients reporting no comorbidities with clear and acute symptomatology but no or little medication are warranted. However, such patients are not only difficult to recruit, they also do not represent the majority of the patient population. For example, about half of the patients with psychiatric disorders were shown to fulfill the criteria of

at least one additional mental disorder and this rate is higher for more severely affected patients (Kessler et al., 2005). Similarly, medication dosage and the number of different drugs are positively correlated with disorder persistence and symptom-load. Hence, patients that are more affected by a disorder also take more medication and for longer periods of time. The interpretation of group differences might therefore be confounded by medication, as both, antidepressants and antipsychotics have been shown to influence reward network activation (Abler et al., 2007; Stoy et al., 2012). Overall, determining inclusion and exclusion criteria for studies in patient populations is a difficult trade-off between experimental control, generalizability of results and of course economic aspects of data acquisition and might account for inconsistent results between clinical studies (e.g., Johnson et al., 2019).

In the presented study the recommendations of Greene and colleagues (2016) were followed and patients with comorbidities were included under certain conditions (e.g., less pronounced or evolved as a consequence of the primary disorder). With respect to medication, a novel standardized composite medication value was computed, in order to account for the great heterogeneity of medication classes and investigated the impact of medication on reward network alterations. In addition, the transdiagnostic and dimensional approach is advantageous as it rules out methodological differences when comparing results between different diagnoses. Prospectively, large-scale, multi-diagnosis research would help to reduce the inconsistencies between smaller-sized studies and enable the comparison of medicated and un-medicated patients and the systematic investigating of current disease states or comorbidities.

3.4.2 Data quality

A second challenge in the investigation of clinical populations is the quality of acquired neuroimaging data, especially with respect to head motion. Patients show increased head motion during fMRI scanning independent of diagnosis (Pardoe, Kucharsky Hiess, & Kuzniecky, 2016; Yao et al., 2017). Motion artifacts result in blurring of the images and impact the signal quality derived from fMRI data (Power et al., 2012, 2014). This is especially true for functional connectivity analyses, where motion increases the proportion of spurious correlations across the brain (Power et al., 2012). Systematic differences in QC parameters, like head motion, can confound the interpretation of results by reducing the sensitivity to find effects of interest and increasing the risk of false positive findings (Makowski, Lepage, & Evans, 2019). As the exclusion of all patients with higher motion ratios reduces not only the sample size but also the generalizability of results,

motion artifacts will inevitably influence the results to some extend (Greene et al., 2016). The lack of clear cut-offs for tolerable motion levels in fMRI analyses leads to inconsistencies between studies and impedes the replicability of results (Makowski et al., 2019). While the impact of motion artifacts depends on a number of factors, for example the research question, data modality, analyzing techniques, there are guidelines on how to deal with motion in clinical populations focusing on 1) the data acquisition and 2) the data analysis steps. During data collection, we implemented procedures that allowed for optimally prepared participants with regards to subjective anxiety and tension in the scanner environment. In addition, a good positioning of participants in the scanner as well as thorough instructions and reminders throughout the experiment helped to reduce motion during data acquisition (Greene et al., 2016). Prospectively, new approaches to improve imaging protocols might further help to assure high data quality in clinical populations, e.g., measuring proactive and real-time measurement of motion during the session using for example the prospective motion correction (PROMO) and frame-wise integrated real-time MRI monitoring (FIRMM). In addition, a reduction of acquisition time might also enhance data quality (Greene et al., 2016). Moreover, there are ways to correct for motion artifacts during data analyses. In our studies, the degree of motion was quantified with the mFD (Power et al., 2012) in order to exclude data with excessive motion, while also testing for systematic differences between patients and controls. Thorough QC procedures were established in both studies including a careful balancing of samples with respect to several quality parameters (e.g., signal-to-noise and signal-to-fluctuation ratio) using an established imaging data quality toolbox (Friedman & Glover, 2006; Simmons, Moore, & Williams, 1999; Weisskoff, 1996). In addition, head motion was included as covariate of no interest and study 1 additionally showed that results were not related to head motion. Overall, using these strategies the risk for spurious findings was minimized, while ensuring sufficient sample sizes.

3.5 Future directions

I believe that both included studies are good examples of how the categorical understanding of reward network alterations in severe mental disorders can be expanded to a more dimensional, multimodal and system-level framework. This adds to current knowledge about the biological mechanisms underlying transdiagnostic reward network alterations, possibly initiating further research developments, some of which are outlined in the following section.

3.5.1 Incorporating dimensional measures of behavioral function

The introduction of RDoC led to an increasing number of clinical neuroimaging studies conducting transdiagnostic studies that specifically investigate dimensional brain-behavior associations (Arrondo et al., 2015; Hägele et al., 2015; Nielsen et al., 2012; Satterthwaite et al., 2015). This is advantageous because the dimensional approach acknowledges the clinical importance of individual differences above and below a categorical threshold (Helzer et al., 2006). In addition, categorical criteria can classify subjects into health and disease groups, while dimensions are better suited to understand the relationship between social and biological variables.

Notably, our studies show that the inclusion of a dimensional symptom severity measure is not trivial and can lead to different mechanistic explanations depending on the investigated diagnostic category. For example, striatal dysfunction has been related to aberrant salience (Gradin et al., 2013), anhedonia (Zhang et al., 2013), social motivation (Chevallier et al., 2012) and behavioral activation (Johnson et al., 2019; Urosević et al., 2008). The selection of dimensional measures should not be limited to disorder-specific measures (e.g., the BDI for depressive symptomatology), which show low variance in healthy subjects and focus on single psychopathological processes, and therefore do not inform whether shared or distinct psychological processes cause the observed alterations. The factor-analytical approach used in study 1 is well-suited to identify such behavioral domains and resembles the main methodology applied in the HiTOP conceptualization of mental disorders.

However, the resulting components of the factor-analytic approach highly depend on the specific test battery. Future studies should try to acquire a comprehensive neuropsychological test battery to ensure a broad coverage of basic function and symptom domains. Ideally, these measures would be used across the research community to ensure replicability and validity of results.

3.5.2 Hierarchization of basic functional domains

Overall, future research would benefit from the introduction of overarching concepts which take into account the complex interactions between basic functioning domains. Both presented studies demonstrate that cognitive processes, normally referred to as Cognitive Systems in the RDoC conceptualization, might influence the Positive Valence System. This is in line with a recently outlined theory, that cognitive control constitutes a domain- and disorder-unspecific pathophysiological mechanism in psychiatric conditions that might help to explain transdiagnostic

alterations (Cole et al., 2014). As outlined above, the authors argue that the experience and regulation of symptoms consumes cognitive resources which limits the flexibility of general cognitive control abilities, leading to domain-specific differences, such as blunted reward network functioning. While the g-factor in the HiTOP conceptualization resembles such a domain-unspecific general disease-factor, the underlying mechanisms of this factor are not described and cognitive processes are not included in this conceptualization. This is surprising given that cognitive dysfunctions are reported across the psychiatric spectrum (Trivedi, 2006) and were shown to genetically overlap with mental disorders (e.g., Hubbard et al., 2016). Within the RDoC framework, a cognitive domain is incorporated as a basic functioning domain including basic cognitive processes, such as attention, perception or cognitive control. In line with the neurocognitive model by Cole and colleagues (2014), our results suggest to expand this framework and incorporate interactions, or even a hierarchization of domains.

In the end, both the traditional diagnostic systems (i.e., ICD-11, DSM-V) as well as modern approaches (i.e., RDoC, HiTOP) are aiming for a descriptive, mutually exclusive classification of highly complex and interacting processes. This simplification of classifying symptoms or functions has the advantage of increasing consistency, transparency, efficiency and applicability of psychiatric nosology. However, it comes with the drawback of neglecting mutual inferences of symptoms or functions, reducing its explanatory power of underlying biological mechanisms. The incorporation of bottom-up, explorative, data-driven approaches, and top-down hypothesis driven attempts will be beneficial for the interpretation of transdiagnostic brain functioning alterations. Specifically, in study 1 a more explorative analysis approach was applied which revealed that different and independent processes (i.e., affective, cognitive and social) influence reward network functioning and highlight the role of the executive control network in mediating vST activation differences. In study 2, a candidate phenotype was derived from established disorder-specific theories and tested along multiple levels of analyses. Both approaches add significant knowledge to the understanding of the neurobiological underpinnings of mental disorders and – like the different diagnostic categorization procedures - will be beneficial in the understanding of the Positive Valence System across the psychiatric spectrum.

3.5.3 Prospects for translation to clinical care

One major criticism about the modern attempts to refine psychiatric diagnostic systems is the difficulty to translate findings to everyday clinical practice. While the aim of RDoC was not to

substitute the traditional categorical diagnosis systems but rather to create an overarching research framework that cuts across diagnostic entities (Walter & Müller, 2015), the gap between research results and its impact on the treatment of mental disorders is still huge (Scarpazza et al., 2020). Within this thesis we replicated the well-established observation of blunted reward network activation across severe mental disorders, most prominently in psychotic disorders. Future studies should move forward to test vST-functioning in the course of the disorder and investigate possible treatment ideas on how to normalize reward network alterations, some of which are introduced in the following section. The most direct manipulation of vST activation activation would be the attempt to upregulate blunted reward network activation, while more indirect approaches could focus on ameliorating reward network dysfunction using medical or psychotherapeutic approaches.

Neurofeedback training of vST activation

Real-time neurofeedback aims at training participants to obtain voluntary control of brain activity or connectivity patterns. Specifically, subjects are presented with changes in their BOLD response in a specific brain region measured with fMRI and are instructed to increase or decrease brain activation. Substantial evidence indicates that subjects can successfully manipulate brain activation throughout the brain (for an overview see Emmert et al., 2016), including cortical (e.g., the ACC, inferior frontal cortex) and subcortical regions (e.g., amygdala or vST). However, the number of studies focusing on reward-related brain regions is small. This might be due to technical challenges, as the vST is a very small, irregular region and shows only short bursts of activity resembling phasic dopamine bursts (Knutson & Gibbs, 2007). Nonetheless, two studies reported that healthy subjects are able to upregulate reward-related brain activation in the vST (Greer, Trujillo, Glover, & Knutson, 2014) and the VTA (Sulzer et al., 2013). However, Greer and colleagues (2014) pointed out that training effects didn't persist after the removal of feedback and conclude that more intense and repeated training sessions might be necessary to obtain longer-lasting training effects. Only one study focused on patient populations and showed that heavy non-addictive social drinkers can successfully learn to downregulate vST activation when presented with alcohol cues (Kirsch et al., 2016). While the idea of treating mental disorders with a non-invasive technique that enables patients to achieve endogenous control over their dopamine system is appealing, many open questions and most importantly a lack of clinical studies impedes an overall evaluation about effectiveness and efficiency of neurofeedback in the vST which is a promising target for future studies.

Development of medication targeting the dopamine regulation circuitry

Current antipsychotic drugs focus mainly on the dopaminergic system and the reduction of positive symptoms, while negative and cognitive symptoms only respond poorly to these medications (Howes et al., 2015). Based on preclinical research, study 2 showed blunted functional coupling between the vST and the hippocampus during reward processing specifically in psychotic patients. This is in line with a recent study by Kätzel and colleagues (2020), who suggested that the mainly glutamatergic circuit, centrally involving the hippocampus, modulates the mesolimbic dopaminergic output and might be a novel target for treating SZ especially in the early stages of the disorder. The regulatory role of the glutamatergic system on the dopamine system is under intense debate (e.g., Howes et al., 2015; Howes & Kaar, 2018) and no therapeutic application is available. However, existing drug targets are currently tested (for an overview see Kätzel et al., 2020), which aim to normalize hippocampal hyperactivity, a well-established observation in SZ (Haukvik et al., 2018; Heckers & Konradi, 2015; Roeske et al., 2020). Studies suggested that the therapeutic treatment of hippocampal dysfunction associated with maladaptive learning processes underlying the aberrant attribution of salience, is most promising in early disease stages (Kätzel et al., 2020). Overall, many open questions remain regarding the ability to normalize reward network alteration, but also the timing of treatment, the interaction of affected brain regions involved over the course of SZ (e.g., the prefrontal cortex or ACC), the functional roles of specific sub-regions in the hippocampus and the overall heterogeneity of disease manifestations (Kätzel et al., 2020).

Psychotherapy targeting the enhancement of cognitive control abilities

The dimensional results in both presented studies suggest that domain-unspecific cognitive functioning abilities influence and possibly mediate alterations in reward network functioning. In line with the above outlined theoretical framework introduced by Cole and colleagues (2014), this could reflect a reduction of cognitive control abilities which are needed to regulate the experienced symptoms. This would indicate that subjects with high cognitive control abilities can cope with a higher symptom load, while subjects with low cognitive capacities will already be affected by comparatively low levels of symptoms. Future studies are warranted to investigate whether patients with high vs. low cognitive control abilities differ with respect to blunted reward network functioning. At the same time, increasing cognitive control abilities by specific therapeutic treatments might alleviate perceived symptoms and compensate domain-specific differences, such as blunted vST activation. This idea is at the heart of the transdiagnostic

metacognitive therapies (e.g., Moritz & Woodward, 2007; Wells & Matthews, 1994). These psychological treatment approaches specifically train the knowledge and awareness of one's cognitive processes, including thoughts and feelings, in order to enhance metacognitive capacities (Moritz & Woodward, 2007; Philipp et al., 2019). Thereby, the increased flexibility to regulate cognitive processes such as attention, monitoring and cognitive control, has been found to reduce individual symptoms (Philipp et al., 2019). While metacognitive therapies have been shown to be efficient in the treatment of mental disorders such as SZ and MD (Philipp et al., 2019), studies investigating the neurobiological correlates are limited (Kowalski, Wypych, Marchewka, & Dragan, 2019; Winter et al., 2019).

The shift of neurobiological models of mental disorders to a transdiagnostic and dimensional conceptualization parallels the development of "third wave" therapies such as metacognitive therapy, which focus on the basic processes and functions of cognition and emotion. It seems that the transdiagnostic neurobiological models (e.g., Cole, et al., 2014) and psychotherapy development (e.g., Wells & Matthews, 1994) might already share more commonalities than generally assumed. Studies across disciplines are warranted to unravel these possibly shared underpinnings in order to bridge the gap between clinical practice and basic neurobiological research. Given the consistently observed associations between cognitive functioning and both, reward-related blunted vST activation and vST-hippocampus coupling, it would be interesting to investigate whether a successful metacognitive therapy could normalize reward network functioning in mental disorders.

4 SUMMARY

The development of valid and feasible dimensional models of diagnostic classification on psychopathology engaged the psychiatric research community for the last decades. One influential research framework, the Research Domain Criteria initiative, characterizes mental functioning along basic domains. One domain implicated in a broad range of psychiatric conditions is the Positive Valence System which summarizes responses to positive motivational stimuli and subsumes different sub processes, such as reward responsiveness, reward anticipation, reward learning and reward valuation. Specifically, alterations in reward anticipation, centrally involving the ventral striatum, are a well-established observation in a range of psychiatric disorders, including schizophrenia, bipolar disorder, major depressive disorder and autism spectrum disorder. This thesis investigated reward anticipation across mental disorders and focused on the relationship between transdiagnostic, categorical and dimensional approaches to psychiatric nosology. Specifically, the comparison of reward network alterations between distinct disorder groups was supplemented by investigating dimensional brain-behavior relationships, system-level circuit abnormalities and a novel potential endophenotype for psychosis.

Both presented studies consistently observed categorical group differences in ventral striatal activation during reward anticipation between healthy controls and patients with severe mental disorders, most prominently on the psychosis end of the extended moods-psychosis spectrum. This provides further evidence to the transdiagnostic relevance of this phenotype. In order to investigate whether shared or distinct psychological processes lead to the observed alterations, we applied a data-driven, explorative approach in study 1 and showed that neurocognitive behavioral measures covering aspects of affective, cognitive and social functioning were dimensionally and transdiagnostically related to markers of altered reward network processing. These results suggest that distinct brain-behavior relationships exist across nosological boundaries which point to shared underlying neural mechanisms and challenge more disorder-specific mechanistic theories of ventral striatal dysfunction.

Extending on these more explorative findings, study 2 used a more hypothesis-driven approach and proposed a new endophenotype for schizophrenia. In line with preclinical models of psychosis the activation of the reward system induced an overall reduction of functional connectivity between the ventral striatum and the hippocampus in psychotic but not mood disorders, that 1) was reduced in first-grade relatives with psychotic but not mood disorders, 2) related to polygenic

risk scores for schizophrenia in a subset of healthy subjects, and 3) was associated with behavioral dimensions of positive and cognitive but not negative symptoms. This study provides evidence that ventral striatal-hippocampus coupling during reward processing is an endophenotype for psychotic disorders and relates to dimensional, clinically meaningful behavioral domains across the psychiatric spectrum.

Interestingly, both studies showed associations between blunted reward network functioning and indicators of cognitive performance measures (i.e., general cognitive functioning and memory performance) highlighting the role of cognitive abilities for transdiagnostic reward network alterations. In line with neurocognitive models of mental disorders this might suggest that cognitive control constitutes a domain- and disorder-unspecific pathophysiological mechanism in psychiatric conditions that might help to explain domain-specific transdiagnostic alterations, such as blunted reward network functioning.

Future studies are warranted to further build on our findings. First, large-scale, pre-registered, multi-site and multi-diagnosis research can reduce the inconsistencies between smaller-sized studies. Second, studies should further improve imaging protocols and ensure high data quality and comparability of patient and control data. Third, investigators should incorporate dimensional, behavioral measures using a comprehensive and ideally consistent neuropsychological test battery that also allows a hierarchization of basic functioning domains with a specific focus on cognitive functioning. Overall, I believe that the presented results add to current disorder-specific mechanistic theories of ventral striatum dysfunction, can inform the development of pharmacological and therapeutic interventions and show the value of combining the strengths of traditional and modern attempts to classify mental disorders.

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